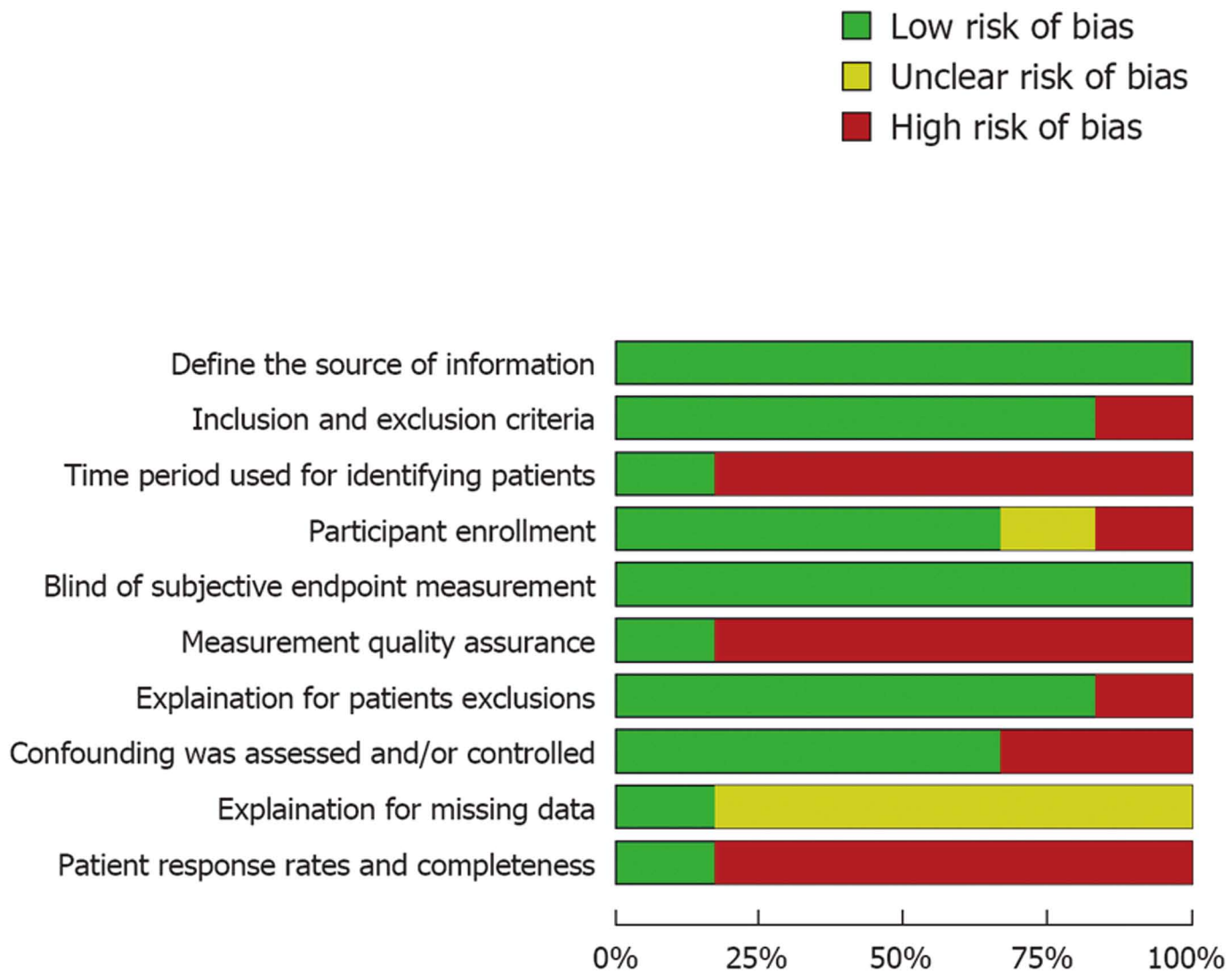
ISSN 2308-3840 (online)

# World Journal of *Meta-Analysis*

*World J Meta-Anal* 2013 August 26; 1(2): 57-96

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World Journal of Meta-Analysis

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Quarterly Volume 1 Number 2 August 26, 2013

**META-ANALYSIS**

*World Journal of Meta-Analysis*
**Volume 1 Number 2 August 26, 2013**

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NAME OF JOURNAL
*World Journal of Meta-Analysis*

ISSN
ISSN 2308-3840 (online)

LAUNCH DATE
May 26, 2013

FREQUENCY
Quarterly



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PUBLISHER
Baishideng Publishing Group Co., Limited
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai,
Hong Kong, China
Fax: +852-6555-7188
Telephone: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
August 26, 2013



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doi:10.13105/wjma.v1.i2.57

*World J Meta-Anal* 2013 August 26; 1(2): 57-77
ISSN 2308-3840 (online)


META-ANALYSIS

# Dose-response relationship of lung cancer to amount smoked, duration and age starting

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Author contributions: Lee PN, Fry JS and Forey BA planned the study; Literature searches were carried out by Coombs KJ, assisted by Lee PN and Forey BA; Data entry was carried out by Coombs KJ and checked by Forey BA, or carried out by Forey BA and checked by Lee PN; Where appropriate, difficulties in interpreting published data or in the appropriate methods for derivation of RRs were discussed by Forey BA and Lee PN; The statistical analyses were conducted by Fry JS along lines discussed and agreed with Lee PN; Lee PN and Fry JS jointly drafted the paper, which was critically reviewed by Forey BA and Coombs KJ.
Supported by Philip Morris Products SA
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Received: April 2, 2013 Revised: May 9, 2013
Accepted: August 4, 2013
Published online: August 26, 2013

## Abstract

**AIM:** To quantify smoking/lung cancer relationships accurately using parametric modelling.

**METHODS:** Using the International Epidemiological Studies on Smoking and Lung Cancer database of all epidemiological studies of 100+ lung cancer cases published before 2000, we analyzed 97 blocks of data for amount smoked, 35 for duration of smoking, and 27 for age started. Pseudo-numbers of cases and controls (or at risk) estimated from RRs by dose level formed the data modelled. We fitted various models relating $\log_e$ RR to dose (d), including $\beta d$, $\beta d^{\gamma}$ and $\beta \log_e (1 + \omega d)$, and investigated goodness-of-fit and heterogeneity between studies.

**RESULTS:** The best-fitting models for $\log_e$ RR were $0.833 \log_e [1 + (8.1c/10)]$ for cigarettes/d (c), $0.792 (y/10)^{0.74}$ for years smoked (y) and $0.176 [(70 - a)/10]^{1.44}$ for age of start (a). Each model fitted well overall, though some blocks misfitted. RRs rose from 3.86 to 22.31 between c = 10 and 50, from 2.21 to 13.54 between y = 10 and 50, and from 3.66 to 8.94 between a = 30 and 12.5. Heterogeneity ($P < 0.001$) existed by continent for amount, RRs for 50 cigarettes/d being 7.23 (Asia), 26.36 (North America) and 22.16 (Europe). Little heterogeneity was seen for duration of smoking or age started.

**CONCLUSION:** The models describe the dose-relationships well, though may be biased by factors including misclassification of smoking status and dose.



**Key words:** Smoking; Lung neoplasms; Dose-response; Meta-analysis; Review; Amount smoked; Duration of smoking; Age at starting to smoke

**Core tip:** This paper, for the first time, meta-analyses smoking/lung cancer dose-relationships. Based on data from 71 studies published before 2000, single parameter models were fitted to summarize how the RR increased with increasing amount smoked, longer duration of smoking, and earlier age of starting to smoke. Overall, the models fitted well. Little heterogeneity was seen for duration of smoking or age of start, but the rise in RR with amount smoked was much steeper in North America and Europe than in Asia. The fitted models can be used to more precisely estimate the lung cancer risk from smoking.

Fry JS, Lee PN, Forey BA, Coombs KJ. Dose-response relationship of lung cancer to amount smoked, duration and age starting. *World J Meta-Anal* 2013; 1(2): 57-77 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i2/57.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i2.57

## INTRODUCTION

We recently carried out a systematic review[1] of the evidence relating smoking to lung cancer incorporating all 287 studies published before 2000 involving a minimum of 100 lung cancer cases. We refer to this as "our earlier review". In that review, we assessed evidence concerning amount smoked per day, duration of smoking, and age of starting to smoke. Data are typically available as blocks of RRs for differing levels of the dose-response measure, each compared to never smokers. Comparing meta-analysis estimates for low, medium and high exposure, we clearly demonstrated a dose-response existed. For example, for amount smoked by current smokers, random-effects RR estimates are 4.71 (95%CI: 4.14-5.37, $n$ = 86) for about 5 cigs/d, 9.83 (95%CI: 8.60-11.24, $n$ = 54) for about 20 cigs/d, and 17.10 (95%CI: 14.62-19.99, $n$ = 62) for about 45 cigs/d. Here "about 5 cigs/d" combined results for dose ranges including 5 but not 20 cigs/d, "about 20 cigs/d" considered ranges including 20 but not 5 or 45 cigs/d, and "about 45 cigs/d" ranges including 45 but not 20 cigs/d. This approach has limitations. First, formal statistical comparison of the RRs at the different levels is not possible as the RRs are not independent, having the same denominator. Second, the analyses do not use all the information available. Thus, results for ranges wholly between 5 and 20 cigs/d or wholly between 20 and 45 cigs/d are ignored, as are results for ranges covering two or more of the "key values" of 5, 20 and 45 cigs/d. Also, linearity, or other shapes of the relationship, is not assessed. Dose-response relationships for years quit are considered in a separate paper[2].

Here, we study dose-response in more detail by fitting models to the various dose-response blocks to estimate parameters which can be meta-analyzed and used to assess heterogeneity. We follow the approach previously used[3] to quantify the dose-response relationship between environmental tobacco smoke exposure and lung cancer risk, developing a variant of it for age of starting. We restrict attention to the data considered in our earlier review[1]. Rather than also considering results for ever smokers, we restrict attention to current smokers, giving a more homogeneous dataset and one showing a stronger dose-relationship. All our analyses are of overall lung cancer risk, no attempt being made in the present paper to fit models for specific histological types.

## MATERIALS AND METHODS

### The International Evidence on Smoking and Lung Cancer database

All analyses use the International Evidence on Smoking and Lung Cancer database, fully described in our earlier review[1]. Papers considered were published before 2000, described studies of 100+ cases, and provided RR estimates for one or more smoking indices. We use the term RR generically to describe alternative RR estimates, *e.g.*, odds ratio or hazard ratio. Lee *et al*[1] gives details of the structure and data entry rules for the database.

### Data selection and blocks

The data considered here comprise blocks of RRs, each relative to never smokers, for all lung cancer (or occasionally near equivalent definitions, each including squamous cell carcinoma and adenocarcinoma) for three measures of dose-response among current smokers: amount smoked, duration and age of starting. Where possible, blocks by sex or by sex and race were considered. Except for amount smoked, blocks by age were considered, if available. Covariate-adjusted RRs were preferred to unadjusted RRs. Each block includes an estimate of the RR and 95%CI: for each level of the measure. The data recorded per block included study type, sex, location, publication year, age range (at baseline for prospective studies), product smoked [any product, cigarettes +/- other products (*i.e.*, pipes, cigars), cigarettes only], never smoker definition (never any product, never cigarettes). For each RR, the range of the measure was also recorded.

### Pseudo-numbers

We used the method of Hamling *et al*[4] on each block to estimate the pseudo-table of numbers of cases, and either controls (for case-control studies) or at risk (for prospective studies) which correspond to the observed RRs and 95%CIs. The method was applied even to unadjusted RRs. This estimation requires, in addition to the given RRs and 95%CIs, estimates of the proportion of never smokers among the controls/at risk and of the ratio of total controls/at risk to total cases, as well as starting values for the numbers of never smoking cases and controls/at risk. These estimates were also recorded on the database. The pseudo-table forms the basic data for fitting the models used, and estimating the overall current smoking RR.

### Midpoints for levels of exposure

For amount smoked, midpoint estimates for each exposure level were derived using standard distributions, as described by Fry *et al*[3] when relating lung cancer risk to amount smoked by the husband. For US studies, the distribution derived from published data for two large CPS I and CPS II studies[5], while for non-US studies, it was that given in Appendix III of International Smoking Statistics[6,7].

For duration of smoking and age of starting the midpoints were based on US NHANES III[8], selecting data for subjects for the given sex, age and range of values of the relevant dose-response measure.

### Statistical models

For each measure, the data analyzed consist of blocks, each containing the pseudo-numbers and the estimated midpoint exposures for each of $\ell$ exposure levels, and for never smokers. The methodology varies by dose-response measure, as described below.

**Table 1 Models used to relate risk to dose**

| | | | |
|---|---|---|---|
| $\log_e$ (RR) | = | $\beta_1 d$ | (linear) |
| $\log_e$ (RR) | = | $\beta_1 d + \beta_2 d^2$ | (quadratic) |
| $\log_e$ (RR) | = | $\beta_1 d + \beta_2 d^2 + \beta_3 d^3$ | (cubic) |
| $\log_e$ (RR) | = | $\beta_1 d^Y$ | (power) |
| $\log_e$ (RR) | = | $\beta_1 \log_e$ (d) | (log) |
| $\log_e$ (RR) | = | $\beta_1 \exp_e$ (d) | (exponential) |
| $\log_e$ (RR) | = | $\beta_1 \log_e$ (1 + Wd) | (log-with-baseline) |

### Amount smoked

The Greenland and Longnecker method[9,10] was used to fit functional forms relating RR to dose (midpoint amount smoked). We fitted the models expressing dose, d, in units of 10 cigs/d.

In the simplest application, the RR is predicted by $\log_e$ RR (d) = βd, β and SE (β) are estimated separately per block, and estimates of β and SE (β) are then combined using inverse-variance weighted random-effects or fixed-effects meta-analysis[11]. This model implies that a fixed dose increment increases risk by a fixed factor. The method can be used with d replaced by a function of d, such as $d^{1/2}$, $d^2$, or log (d + 1).

Greenland *et al*[9] describe a more general, "pool-first", method in which all the blocks are considered in a single analysis. The method gives the same results for the model log RR = βd, but allows direct fitting for other functional forms.

As the best model was initially unclear, we first tried various models (Table 1) using the pool-first method, comparing deviances to assess which models fitted the overall data better. For the "power" and "log-with-baseline" models, the parameters Y or W could not be fitted directly, but an iterative method was adopted, comparing deviances for a range of values.

For the models with lowest deviance, the simpler approach was then used to estimate $\beta_1$ (and $\beta_2$, $\beta_3$) and its standard error (SE) for each block. For a particular model, goodness-of-fit for a block was tested by comparing observed and fitted number of cases (and for case-control studies also the observed number of controls) at each level of amount smoked (including never smokers). The fitted values were estimated as described in Goodness of fit[11]. As also described there, the sum of (observed - fitted)$^2$/fitted over levels was taken as an approximate chi-squared on ℓ - 1 degrees of freedom (df) for prospective studies or on 2ℓ - 1 df for case-control studies. Information on overall goodness-of-fit was derived by summing observed and fitted values over blocks for never smokers and for specified levels of amount smoked, and similarly deriving an approximate chi-squared statistic. Plots of observed and predicted RRs per block were also examined.

### Duration of smoking

The approach used was as for amount smoked.

### Age of starting to smoke

For smokers of a given age, age of starting (a) and duration (y) are directly related. We used the same basic approach, replacing y by 70 - a to produce a duration-like measure. As this produced a relatively good fit, we did not attempt sensitivity analyses replacing y by 60 - a or 80 - a.

### Regression analyses

Sources of heterogeneity were studied by inverse-variance weighted regression of β. Between block variation was examined one factor at a time (simple regression), and using forward stepwise methods. The factors used were study type, sex, location, publication year, midpoint age (at baseline for prospective studies), smoking product and study size. The deviance of the fitted models indicated the extent to which heterogeneity was explained.

### Statistical analysis

No multiple testing adjustments were made, significant being defined as $P < 0.05$. However, results showing stronger evidence of a relationship ($P < 0.01$, or $P < 0.001$), and sometimes weaker evidence ($P < 0.1$) are also distinguished, where appropriate. All data entry and most statistical analyses were carried out using ROELEE version 3.1 (available from PN Lee Statistics and Computing Ltd., 17 Cedar Road, Sutton, Surrey SM2 5DA, United Kingdom). Some analyses used Excel 2003.

## RESULTS

### Studies considered

For each of the 71 studies providing the data used, Studies[11], gives the six character reference code (REF); a brief description incorporating the location, characteristics of the population studied, study design, and study duration; the total number of lung cancers studied; and the measures for which data are analyzed.

### Amount smoked

Details of blocks used for each measure are given in Blocks[11]. These include study REF, sex (and where applicable race), study type, location, product smoked, definition of unexposed group, adjustment factors used, current smoker RR, and total numbers of cases in smokers.

The 97 blocks derive from 69 studies, 45 providing results for a single block, 22 results by sex, and 2 (DORGAN and HUMBLE) results by sex and race. 55 blocks (56.7%) are for males, 34 (35.1%) females, and 8 (8.2%) both sexes. 48 (49.5%) are from prospective studies. 43 (44.3%) are from North American studies, 32 (33.0%) from Europe and 17 (17.5%) from Asia, the remaining 5 (5.2%) from South America, Africa or Australasia. Five different combinations of product *vs* unexposed occur: cigarettes ± other products *vs* never any product (32 blocks 33.0%), cigarettes ± other products *vs* never cigarettes (29, 29.9%), any product *vs* never any product (20, 20.6%), cigarettes only *vs* never any product (13, 13.4%) and cigarettes only *vs* never cigarettes for (3, 3.1%). Of the 8 blocks for sexes combined, 4 (50.0%) concern RRs adjusted for sex, while 64 of the full 97 blocks (66.0%)

**Table 2 Amount smoked by current smokers (cigarettes per day) - dose-response data**

| Block: Study | Amount smoked groupings[1] | Mean values | RRs[2] |
|---|---|---|---|
| 1: AKIBA | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 3.50, 6.10, 19.10 M |
| 2: AKIBA | 1-14, 15+ | 8.11, 24.09 | 3.60, 5.80 M |
| 3: ARCHER | 1-19, 20, 21+ | 10, 20, 31.83 | 3.53, 6.09, 8.52 M |
| 4: AXELSS | 20 | 20 | 43.30 |
| 5: BENSHL | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 4.00, 9.05, 10.95 M |
| 6: BEST | 1-9, 10-20, 21+ | 4.85, 15.92, 31.83 | 10.00, 16.41, 17.31 M |
| 7: BOUCOT | 1-20, 21-40, 41+ | 13.38, 29.02, 53.33 | 54.09, 78.56, 161.70 M |
| 8: BRETT | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 2.55, 4.25, 8.00 M |
| 9: BROSS | 1-20, 21+ | 13.38, 31.83 | 4.91, 7.20 M |
| 10: BUFFLE | 1-19, 20, 21+ | 10.20, 31.83 | 5.60, 11.84, 22.10 M |
| 11: CEDERL | 1-7, 8-15, 16+ | 4.29, 11.61, 25.41 | 3.40, 7.50, 11.90 M |
| 12: CEDERL | 1-7, 8-15, 16+ | 4.29, 11.61, 25.41 | 2.83, 7.74, 7.56 |
| 13: CHANG | 1-10, 11-20, 21+ | 7.08, 17.67, 31.83 | 5.02, 10.60, 8.26 |
| 14: CHANG | 1-10, 11-20, 21+ | 7.08, 17.67, 31.83 | 3.03, 4.87, 8.21 M |
| 15: CHOW | 1-19, 20-29, 30+ | 10, 21.35, 38.39 | 13.88, 21.87, 44.48 M |
| 16: COMSTO | 1-19, 20-39, 40+ | 10, 22.90, 45.71 | 12.42, 18.16, 24.92 M |
| 17: COMSTO | 1-19, 20-39, 40+ | 10, 22.90, 45.71 | 7.45, 17.35, 13.27 |
| 18: CORREA | 1-20, 21+ | 13.38, 31.83 | 9.30, 25.30 M |
| 19: CPSI | 1-9, 10-19, 20-39, 40+ | 4.85, 12.73, 22.90, 45.71 | 4.51, 8.41, 14.30, 17.49 M |
| 20: CPSII | 1-9, 10-19, 20, 21-39, 40, 41+ | 4.85, 12.73, 20, 26.71, 40, 53.33 | 12.22, 14.52, 21.59, 22.72, 24.14, 45.52 M |
| 21: CPSII | 1-9, 10-19, 20, 21-39, 40, 41+ | 4.85, 12.73, 20, 26.71, 40, 53.33 | 3.89, 8.33, 14.21, 21.40, 19.31, 18.22 |
| 22: DARBY | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 73.47, 95.43, 142.69 M |
| 23: DARBY | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 15.70, 21.50, 41.62 M |
| 24: DEAN3 | 1-12, 13-22, 23+ | 7.65, 18.42, 33.04 | 5.46, 7.42, 21.66 M |
| 25: DEAN3 | 1-12, 13-22, 23+ | 7.65, 18.42, 33.04 | 3.16, 8.42, 24.24 M |
| 26: DEKLER | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 19.40, 23.00, 32.50 M |
| 27: DOLL2 | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 5.20, 10.60, 22.40 M |
| 28: DOLL2 | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 1.29, 6.43, 29.71 M |
| 29: DORANT | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 8.52, 27.22, 36.24 M |
| 30: DORGAN | 1-19, 20+ | 10, 26.03 | 9.13, 20.65 M |
| 31: DORGAN | 1-19, 20+ | 10, 26.03 | 26.67, 72.46 M |
| 32: DORGAN | 1-19, 20+ | 10, 26.03 | 6.55, 24.13 M |
| 33: DORGAN | 1-19, 20+ | 10, 26.03 | 7.43, 41.43 M |
| 34: DORN | 1-9, 10-20, 21-39, 40+ | 4.85, 15.92, 26.71, 45.71 | 4.02, 9.92, 17.19, 22.75 M |
| 35: ENGELA | 1-4, 5-9, 10-14, 15-19, 20+ | 2.5, 6.5, 10.88, 15.83, 26.03 | 1.40, 4.10, 7.00, 11.00, 15.00 M |
| 36: ENGELA | 1-4, 5-9, 10-14, 15+ | 2.5, 6.5, 10.88, 24.09 | 12.00, 12.00, 24.00, 26.00 |
| 37: ENSTRO | 1-9, 10-19, 20, 21-39, 40+ | 4.85, 12.73, 20, 26.71, 45.71 | 4.74, 7.68, 13.65, 16.08, 19.41 M |
| 38: ENSTRO | 1-9, 10-19, 20, 21+ | 4.85, 12.73, 20, 31.83 | 2.15, 4.31, 9.48, 16.47 M |
| 39: GAO2 | 1-19, 20-29, 30+ | 10, 21.35, 38.39 | 3.36, 7.54, 10.63 M |
| 40: GILLIS | 1-14, 15-24, 25-34, 35-49, 50+ | 8.11, 19.19, 28.13, 39, 53.33 | 4.50, 7.60, 8.60, 9.70, 7.80 |
| 41: HAENSZ | 1-20, 21+ | 13.38, 31.83 | 1.77, 5.15 M |
| 42: HAMMO2 | 1-19, 20+ | 10.00, 26.03 | 9.15, 10.39 M |
| 43: HAMMON | 1-9, 10-20, 21-39, 40+ | 4.85, 15.92, 26.71, 45.71 | 7.44, 8.42, 17.91, 20.64 M |
| 44: HIRAYA | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 2.06, 4.00, 6.24 M |
| 45: HIRAYA | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 2.25, 2.56, 4.47 M |
| 46: HITOSU | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 2.08, 2.82, 4.68 M |
| 47: HITOSU | 1-14, 15+ | 8.11, 24.09 | 3.11, 3.17 M |
| 48: HOLE | 1-14, 15-24, 25-34, 35+ | 8.11, 19.19, 28.13, 44.38 | 5.47, 8.90, 10.75, 7.49 |
| 49: HUMBLE | 1-19, 20+ | 10, 26.03 | 9.20, 24.70 M |
| 50: HUMBLE | 1-19, 20+ | 10, 26.03 | 11.60, 26.10 M |
| 51: HUMBLE | 1-19, 20+ | 10, 26.03 | 19.20, 16.00 |
| 52: HUMBLE | 1-19, 20+ | 10, 26.03 | 18.50, 36.90 M |
| 53: KAISE2 | 1-19, 20+ | 10, 26.03 | 4.47, 10.34 M |
| 54: KAISE2 | 1-19, 20+ | 10, 26.03 | 7.61, 22.12 M |
| 55: KAISER | 1-19, 20-40, 41+ | 10, 24.32, 53.33 | 6.58, 17.24, 20.91 M |
| 56: KAISER | 1-19, 20-40, 41+ | 10, 24.32, 53.33 | 3.42, 7.98, 12.63 M |
| 57: KANELL | 1-10, 11-20, 21-35, 36+ | 7.08, 17.67, 26.71, 45.71 | 1.71, 7.06, 20.39, 34.22 M |
| 58: KATSOU | 1-20, 21+ | 13.38, 31.83 | 2.26, 7.46 M |
| 59: KAUFMA | 1-14, 15-24, 25-34, 35-44, 45+ | 8.11, 19.19, 28.13, 39, 53.33 | 8.00, 15.00, 28.00, 43.00, 60.00 M |
| 60: KINLEN | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 10.61, 14.14, 21.74 M |
| 61: KNEKT | 1-14, 15+ | 8.11, 24.09 | 5.00, 12.70 M |
| 62: KOO | 1-10, 11-20, 21-30 | 7.08, 17.67, 25.88 | 1.36, 7.29, 1.52 |
| 63: LIAW | 1-10, 11-20, 21+ | 7.08, 17.67, 31.83 | 3.10, 3.60, 8.30 M |
| 64: LIDDEL | 1-19, 20+ | 10, 26.03 | 3.33, 5.02 M |
| 65: MACLEN | 1-9, 10-19, 20-29, 30+ | 4.85, 12.73, 21.35, 38.39 | 1.36, 3.41, 4.16, 5.00 M |
| 66: MACLEN | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 0.76, 3.44, 3.84 |
| 67: MATOS | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 1.60, 8.00, 15.00 M |

| | | | |
|---|---|---|---|
| 68: MIGRAN | 1-9, 10-19, 20, 21+ | 4.85, 12.73, 20, 31.83 | 4.01, 4.24, 5.14, 5.93 M |
| 69: MIGRAN | 1-9, 10-19, 20 | 4.85, 12.73, 20 | 4.88, 6.53, 7.48 M |
| 70: MRFITR | 1-19, 20-39, 40+ | 10, 22.90, 45.71 | 10.86, 50.12, 56.43 M |
| 71: NAM | 1-24, 25+ | 14.06, 34.63 | 6.70, 10.27 M |
| 72: NAM | 1-24, 25+ | 14.06, 34.63 | 9.06, 16.65 M |
| 73: PARKIN | 1-14, 15+ | 8.11, 24.09 | 3.90, 5.20 M |
| 74: PERSH2 | 1-9, 10+ | 4.85, 20.90 | 5.76, 11.34 M |
| 75: PETO | 1-14, 15+ | 8.11, 24.09 | 5.50, 9.49 M |
| 76: PEZZO2 | 1-20, 21-40, 41+ | 13.38, 29.02, 53.33 | 8.00, 44.39, 112.13 M |
| 77: PEZZOT | 1-20, 21-40, 41+ | 13.38, 29.02, 53.33 | 7.40, 70.00, 246.50 M |
| 78: PRESCO | 1-14, 15+ | 8.11, 24.09 | 10.20, 19.96 M |
| 79: PRESCO | 1-14, 15+ | 8.11, 24.09 | 6.36, 10.08 M |
| 80: SEGI2 | 1-9, 10-19, 20-29, 30-39, 40+ | 4.85, 12.73, 21.33, 31.07, 45.71 | 2.10, 3.10, 3.40, 6.90, 7.90 M |
| 81: SEGI2 | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 2.90, 1.44, 1.03 |
| 82: SHAW | 1-19, 20+ | 10, 26.03 | 6.31, 30.48 M |
| 83: SOBUE | 1-19, 20-29, 30+ | 10, 21.35, 38.39 | 3.52, 4.00, 4.55 M |
| 84: SPEIZE | 1-4, 5-14, 15-24, 25-34, 35+ | 2.5, 9.42, 19.19, 28.13, 44.38 | 2.70, 5.20, 12.60, 15.70, 22.00 M |
| 85: STOCKW | 1-19, 20-40, 41+ | 10, 24.32, 53.33 | 6.67, 14.51, 28.84 M |
| 86: SVENSS | 1-10, 11-20, 21+ | 7.08, 17.67, 31.83 | 4.60, 12.60, 59.00 M |
| 87: TENKAN | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 15.86, 20.25, 24.97 M |
| 88: TSUGAN | 1-15, 16-35, 36+ | 9.33, 22.45, 45.71 | 0.90, 1.22, 1.66 |
| 89: TULINI | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 6.02, 12.00, 27.30 M |
| 90: TULINI | 1-14, 15-24, 25+ | 8.11, 19.19, 34.63 | 8.17, 26.30, 38.70 M |
| 91: TVERDA | 1-9, 10-19, 20+ | 4.85, 12.73, 26.03 | 2.14, 3.32, 6.56 M |
| 92: TVERDA | 1-9, 20+ | 4.85, 26.03 | 4.53, 18.00 M |
| 93: WAKAI | 1-19, 20-20, 30+ | 10.00, 21.35, 38.39 | 1.80, 4.01, 9.19 M |
| 94: WU | 1-20, 21+ | 13.38, 31.83 | 3.25, 8.48 M |
| 95: WYNDE6 | 1-10, 11-20, 21-30, 31+ | 7.08, 17.67, 25.88, 43.06 | 6.80, 11.16, 17.32, 28.22 M |
| 96: WYNDE6 | 1-10, 11-20, 21-30, 31+ | 7.08, 17.67, 25.88, 38.39 | 3.75, 11.97, 21.64, 39.14 M |
| 97: YAMAGU | 1-20, 21+ | 13.38, 31.83 | 3.75, 12.14 M |

[1]In some studies, amount smoked is based on cigarette equivalents for cigars and pipes; [2]M indicates a strictly monotonic rise in RR with increasing amount smoked.

concern age-adjusted RRs. Race and/or other factors were adjusted for in 28 (28.9%) blocks.

Table 2 gives for each block the levels used to categorize amount smoked and the corresponding estimated mean values and RRs for each level. The RRs reveal an obvious trend for risk to rise with amount smoked. Of the 96 blocks with more than one level, 84 (87.5%) show a strictly monotonic increase in RR. However, considerable variation is evident in the RR for the highest exposure.

Table 3 gives the pool-first results investigating model suitability. The exponential model is particularly poor, explaining only 21.75% of the overall deviance in the estimates of log RR. The log model is also relatively poor. The linear, quadratic and cubic models are better. However, despite involving more parameters, the cubic model explains less of the overall deviance than do the best-fitting power or log-with-baseline models. The residual deviance is lowest for the log-with-baseline model, the best-fitting W value explaining 94.12% of the overall deviance, though the best-fitting power model explains almost as much (93.95%).

Fit Amount Smoked[11], gives full details for the further analyses carried out using the linear, and best-fitting power and log-with-baseline models. These include 95%CIs for the RRs in Table 2, and observed and fitted numbers by level for each block.

For each of these models, Table 4 compares the observed and fitted numbers of cases summed over blocks for never smokers and for current smokers by amount smoked. The linear model fits poorly, overestimating cases for never smokers and 30+ cigs/d smokers and underestimating for 1-30 cigs/d smokers, the model implying a far steeper increase with amount smoked than observed. This is consistent with the block-specific goodness-of-fit tests, 63 showing misfits significant at $P < 0.05$. This model is clearly inadequate for amount smoked.

Although Table 4 shows highly significant ($P < 0.001$) misfit to both the power and log-with-baseline models, the misfit is not substantial, with observed and expected numbers generally agreeing to a few percent.

For each block, and both models, Table 5 gives fitted values of $\beta_1$ and SE and goodness-of-fit $P$ values. A number of blocks show significant ($P < 0.05$) misfit, these tending to be the same blocks for both models. We comment on those 15 blocks where the $P$ value for the log-with-baseline model is $< 0.01$ (Fit Amount Smoked[11] and Table 2 for further details). These divide into various categories. Three blocks (19: CPS I , 34: DORN, 37: ENSTRO males) involve very large numbers of cases (Table 3) where the model appears to fit quite well, though in block 19: CPS I the observed flattening of response for 40+ cigs/d is not well fitted. Seven blocks (6: BEST, 20: CPS Ⅱ males, 22: DARBY males, 43: HAMMON, 60: KINLEN, 74: PERSH2, 87: TENKAN) show a marked risk increase for the lowest level of amount smoked, but the slope subsequently flattens. In contrast the reverse is true for five blocks (24: DEAN3 males, 38: ENSTRO fe-

**Table 3 Comparing the suitability of different models relating log *RR* to amount smoked by current smokers, expressed as d = cigarettes per day/10**

| Model | Parameter value[1] | Fitted coefficient(s) (SE) | Deviance | DF | Deviance explained (%) |
|---|---|---|---|---|---|
| Null | - | - | 24894.53 | 97 | |
| Linear: log RR = $\beta_1 d$ | - | $\beta_1$ = 0.6107 (0.0046) | 7265.32 | 96 | 70.82 |
| Quadratic: log RR = $\beta_1 d + \beta_2 d^2$ | - | $\beta_1$ = 1.4121 (0.0130), $\beta_2$ = -0.1792 (0.0027) | 2907.39 | 95 | 88.32 |
| Cubic: log RR = $\beta_1 d + \beta_2 d^2 + \beta_3 d^3$ | - | $\beta_1$ = 2.1915 (0.0266), $\beta_2$ = -0.6346 (0.0138), $\beta_3$ = 0.0633 (0.0019) | 1779.05 | 94 | 92.86 |
| Power: log RR = $\beta_1 d^Y$ | Y = 0.32 | $\beta_1$ = 1.8922 (0.0124) | 1512.49 | 96 | |
| | Y = 0.33 | $\beta_1$ = 1.8691 (0.0122) | 1506.19 | 96 | |
| | Y = 0.34 | $\beta_1$ = 1.8457 (0.0121) | 1506.07 | 96 | 93.95 |
| | Y = 0.35 | $\beta_1$ = 1.8222 (0.0119) | 1511.92 | 96 | |
| | Y = 0.36 | $\beta_1$ = 1.7986 (0.0118) | 1523.54 | 96 | |
| | Y = 0.50 | $\beta_1$ = 1.4673 (0.0097) | 2179.71 | 96 | |
| | Y = 1.00 | $\beta_1$ = 0.6107 (0.0046) | 7265.32 | 96 | |
| | Y = 2.00 | $\beta_1$ = 0.0969 (0.0010) | 14739.19 | 96 | |
| Log: log RR = $\beta_1 \log d$ | - | $\beta_1$ = 1.2265 (0.0107) | 11674.70 | 96 | 53.10 |
| Exponential: log RR = $\beta_1 \exp d$ | - | $\beta_1$ = 0.0120 (0.0002) | 19480.21 | 96 | 21.75 |
| Log-with-baseline: log RR = $\beta_1 \log (1 + Wd)$ | W = 7.5 | $\beta_1$ = 0.8520 (0.0056) | 1466.21 | 96 | |
| | W = 7.7 | $\beta_1$ = 0.8456 (0.0055) | 1465.37 | 96 | |
| | W = 7.9 | $\beta_1$ = 0.8394 (0.0054) | 1464.88 | 96 | |
| | W = 8.0 | $\beta_1$ = 0.8364 (0.0055) | 1464.76 | 96 | |
| | W = 8.1 | $\beta_1$ = 0.8334 (0.0054) | 1464.71 | 96 | 94.12 |
| | W = 8.2 | $\beta_1$ = 0.8305 (0.0054) | 1464.73 | 96 | |
| | W = 8.3 | $\beta_1$ = 0.8277 (0.0054) | 1464.82 | 96 | |

[1]Note that we only sought the best-fitting value of Y to two decimal places and of W to one decimal place.

**Table 4 Amount smoked by current smokers - observed and fitted lung cancers for the linear, best power and best log-with-baseline model, with $\beta_1$ fitted separately for each block**

| Midpoint amount smoked (cigs/d) | Observed[1] | Fitted[2] | | |
|---|---|---|---|---|
| | | Linear model | Best power model | Best log-with-baseline model |
| < 5 | 1249.17 | 1023.00 | 1297.42 | 1173.88 |
| 5 to < 10 | 2579.62 | 2156.31 | 2595.37 | 2539.78 |
| 10 to < 15 | 6125.69 | 4749.92 | 6276.74 | 6299.68 |
| 15 to < 20 | 7940.18 | 6678.14 | 8009.06 | 8156.50 |
| 20 to < 30 | 18138.36 | 15724.45 | 17468.99 | 17678.51 |
| 30 to < 40 | 3858.94 | 4106.12 | 3743.23 | 3701.31 |
| 40+ | 7703.88 | 8860.42 | 8115.77 | 7949.95 |
| Never smoked | 6649.61 | 10947.08 | 6738.86 | 6745.84 |
| Total | 54245.45 | 54245.45 | 54245.45 | 54245.45 |
| Fit statistic[3] | | 3792.53 | 65.29 | 56.78 |

[1]Observed pseudo-number of lung cancer cases, summed over blocks; [2]Fitted pseudo-number of lung cancer cases, summed over blocks. For each study, the fitted number of cases for each block is calculated from the numbers at risk and the fitted RRs by amount smoked, derived from the fitted value of $\beta_1$; [3]Based on summation of (observed-fitted)$^2$/fitted, the summation also including terms for the observed and fitted total numbers of controls (not shown). The statistic can be considered to be approximately chisquared on 12 DF and is significant at $P < 0.001$ for all three models.

males, 57: KANELL, 76: PEZZO2, 77: PEZZOT) with the RR for the highest exposure greater than predicted from the response at lower levels. For some of the 15 blocks, the number of cases in never smokers is relatively low (less than 10 in 6 of them) and the best-fitting model gives rather different fitted numbers, so the fitted block of RRs appears substantially different from that observed For example, in block 6: BEST where the observed pseudo-number of cases in never smokers is 6.88, and the observed RRs are 10.00, 16.41 and 17.31 for 1-9, 10-20 and 21+ cigs/d, the fitted number of cases in never smokers is 23.61 and the fitted RRs are 2.47, 4.46 and 6.47.

Table 6 presents results of weighted simple regression analyses of $\beta_1$ for the log-with-baseline model. There is highly significant ($P < 0.001$) variation by continent, with $\beta_1$ much lower for Asian studies, and by study size, larger studies giving higher $\beta_1$ values. Some variation is also seen for sex ($P < 0.05$), study type, publication year and midpoint age ($P < 0.1$), but not with product definition or unexposed group. Table 6 also presents predicted RRs at 20 cigs/d. The variation by continent is clear.

In a forward stepwise analysis (not shown), continent remained highly significant ($P < 0.001$), but no other factor remained significant at $P < 0.05$. The association with study size seems due to a strong correlation with continent.

**Table 5 Amount smoked by current smokers - fitted values of $\beta_1$ and SE, and *P* values for goodness-of-fit tests for the best-fitting power model and log-with-baseline model**

| Block: Study | Log-with-baseline model[1] log RR = $\beta_1$ [1 + (8.10c/10)] | | | Power model[1] log RR = $\beta_1$ [(c/10)$^{0.34}$] | | |
|---|---|---|---|---|---|---|
| | $\beta_1$ | SE $\beta_1$ | *P* (fit)[2] | $\beta_1$ | SE $\beta_1$ | *P* (fit)[2] |
| 1: AKIBA | 0.6599 | 0.0712 | NS | 1.4882 | 0.1609 | NS |
| 2: AKIBA | 0.6099 | 0.0660 | NS | 1.3445 | 0.1453 | NS |
| 3: ARCHER | 0.6713 | 0.1274 | NS | 1.4932 | 0.2835 | NS |
| 4: AXELSS | 1.3245 | 0.2214 | NS | 2.9770 | 0.4976 | NS |
| 5: BENSHL | 0.7133 | 0.1169 | NS | 1.6337 | 0.2688 | NS |
| 6: BEST | 0.5678 | 0.0824 | 0.0000 | 1.3483 | 0.1948 | 0.0001 |
| 7: BOUCOT | 0.8332 | 0.2140 | NS | 1.7439 | 0.4482 | NS |
| 8: BRETT | 0.6637 | 0.1146 | NS | 1.4946 | 0.2575 | NS |
| 9: BROSS | 0.6090 | 0.0735 | NS | 1.3514 | 0.1634 | NS |
| 10: BUFFLE | 0.9349 | 0.1040 | NS | 2.0810 | 0.2313 | NS |
| 11: CEDERL | 0.8191 | 0.0726 | NS | 1.8388 | 0.1634 | NS |
| 12: CEDERL | 0.7697 | 0.0693 | NS | 1.6833 | 0.1520 | NS |
| 13: CHANG | 0.6772 | 0.1522 | NS | 1.5044 | 0.3402 | NS |
| 14: CHANG | 0.6255 | 0.1165 | NS | 1.3937 | 0.2595 | NS |
| 15: CHOW | 1.0002 | 0.1050 | NS | 2.2134 | 0.2311 | NS |
| 16: COMSTO | 0.8497 | 0.1552 | NS | 1.8491 | 0.3399 | NS |
| 17: COMSTO | 0.8857 | 0.1172 | NS | 1.9560 | 0.2601 | NS |
| 18: CORREA | 0.9945 | 0.0483 | NS | 2.2052 | 0.1069 | NS |
| 19: CPS I | 0.8314 | 0.0348 | 0.0002 | 1.8278 | 0.0773 | 0.0000 |
| 20: CPS II | 0.8262 | 0.0331 | 0.0000 | 1.8467 | 0.0739 | 0.0000 |
| 21: CPS II | 0.8972 | 0.0304 | 0.0153 | 1.9874 | 0.0677 | 0.0006 |
| 22: DARBY | 0.8198 | 0.1213 | 0.0000 | 1.9085 | 0.2770 | 0.0000 |
| 23: DARBY | 1.0879 | 0.0841 | NS | 2.4434 | 0.1879 | NS |
| 24: DEAN3 | 0.8271 | 0.0724 | 0.0009 | 1.8968 | 0.1639 | 0.0042 |
| 25: DEAN3 | 0.8617 | 0.0801 | (0.0569) | 1.9152 | 0.1789 | 0.0368 |
| 26: DEKLER | 0.5704 | 0.1839 | NS | 1.3114 | 0.4155 | NS |
| 27: DOLL2 | 1.0464 | 0.0644 | (0.0824) | 2.3531 | 0.1443 | NS |
| 28: DOLL2 | 1.1001 | 0.1698 | NS | 2.4424 | 0.3745 | 0.0091 |
| 29: DORANT | 1.1082 | 0.0867 | 0.0322 | 2.5183 | 0.1972 | 0.0270 |
| 30: DORGAN | 0.9728 | 0.0937 | NS | 2.1814 | 0.2101 | NS |
| 31: DORGAN | 1.4168 | 0.1835 | NS | 3.1557 | 0.4086 | NS |
| 32: DORGAN | 0.9636 | 0.0595 | NS | 2.1418 | 0.1325 | NS |
| 33: DORGAN | 1.0359 | 0.1844 | NS | 2.2976 | 0.4094 | NS |
| 34: DORN | 0.9024 | 0.0171 | 0.0001 | 2.0099 | 0.0381 | 0.0000 |
| 35: ENGELA | 1.0083 | 0.1270 | NS | 2.3043 | 0.2995 | NS |
| 36: ENGELA | 1.0897 | 0.1561 | 0.0206 | 2.5654 | 0.3553 | NS |
| 37: ENSTRO | 0.8261 | 0.0312 | 0.0000 | 1.7910 | 0.0684 | 0.0000 |
| 38: ENSTRO | 0.8229 | 0.0252 | 0.0000 | 1.8368 | 0.0564 | 0.0000 |
| 39: GAO2 | 0.7037 | 0.1042 | NS | 1.5526 | 0.2304 | NS |
| 40: GILLIS | 0.5811 | 0.0729 | NS | 1.2704 | 0.1614 | NS |
| 41: HAENSZ | 0.3382 | 0.0805 | NS | 0.7563 | 0.1796 | NS |
| 42: HAMMO2 | 0.5198 | 0.1167 | 0.0112 | 1.1870 | 0.2641 | 0.0138 |
| 43: HAMMON | 0.8032 | 0.0748 | 0.0038 | 1.8185 | 0.1677 | 0.0116 |
| 44: HIRAYA | 0.5974 | 0.0337 | NS | 1.3374 | 0.0756 | NS |
| 45: HIRAYA | 0.4424 | 0.0501 | NS | 0.9729 | 0.1100 | NS |
| 46: HITOSU | 0.4573 | 0.1182 | NS | 1.0324 | 0.2654 | NS |
| 47: HITOSU | 0.4988 | 0.1223 | NS | 1.0992 | 0.2686 | NS |
| 48: HOLE | 0.6142 | 0.1082 | NS | 1.3410 | 0.2413 | NS |
| 49: HUMBLE | 1.0435 | 0.1431 | NS | 2.3386 | 0.3207 | NS |
| 50: HUMBLE | 1.0378 | 0.2633 | NS | 2.3306 | 0.5907 | NS |
| 51: HUMBLE | 0.8922 | 0.1393 | NS | 1.9997 | 0.3114 | NS |
| 52: HUMBLE | 1.2268 | 0.2487 | NS | 2.7318 | 0.5532 | NS |
| 53: KAISE2 | 0.7599 | 0.1018 | NS | 1.6991 | 0.2278 | NS |
| 54: KAISE2 | 1.0098 | 0.1107 | NS | 2.2592 | 0.2478 | NS |
| 55: KAISER | 0.7685 | 0.0477 | 0.0247 | 1.6130 | 0.1010 | 0.0033 |
| 56: KAISER | 0.6882 | 0.0570 | NS | 1.4932 | 0.1238 | NS |
| 57: KANELL | 0.8982 | 0.0647 | 0.0000 | 1.9758 | 0.1442 | 0 |
| 58: KATSOU | 0.4517 | 0.1260 | NS | 1.0089 | 0.2809 | NS |
| 59: KAUFMA | 1.0712 | 0.0583 | NS | 2.3560 | 0.1278 | NS |
| 60: KINLEN | 0.6021 | 0.0616 | 0.0017 | 1.3838 | 0.1399 | 0.0055 |
| 61: KNEKT | 0.8644 | 0.1264 | NS | 1.9618 | 0.2876 | NS |
| 62: KOO | 0.4309 | 0.1424 | NS | 0.9299 | 0.3133 | NS |
| 63: LIAW | 0.5538 | 0.0918 | NS | 1.2384 | 0.2045 | NS |
| 64: LIDDEL | 0.5136 | 0.0742 | NS | 1.1535 | 0.1666 | NS |

| | | | | | | |
|---|---|---|---|---|---|---|
| 65: MACLEN | 0.4973 | 0.1511 | NS | 1.0875 | 0.3355 | NS |
| 66: MACLEN | 0.4301 | 0.1161 | NS | 0.9350 | 0.2577 | NS |
| 67: MATOS | 0.8315 | 0.1122 | NS | 1.8390 | 0.2485 | NS |
| 68: MIGRAN | 0.4590 | 0.1448 | NS | 1.0568 | 0.3286 | NS |
| 69: MIGRAN | 0.7246 | 0.2207 | NS | 1.6547 | 0.4987 | NS |
| 70: MRFITR | 0.6382 | 0.2225 | 0.0338 | 1.1984 | 0.4461 | 0.0152 |
| 71: NAM | 0.6883 | 0.0711 | NS | 1.5157 | 0.1569 | NS |
| 72: NAM | 0.8481 | 0.0690 | NS | 1.8809 | 0.1532 | NS |
| 73: PARKIN | 0.6129 | 0.0554 | NS | 1.3556 | 0.1222 | NS |
| 74: PERSH2 | 0.8420 | 0.0381 | 0.0004 | 1.9065 | 0.0854 | 0.0446 |
| 75: PETO | 0.6262 | 0.1606 | NS | 1.4651 | 0.3737 | NS |
| 76: PEZZO2 | 1.3641 | 0.1251 | 0.0051 | 2.9784 | 0.2710 | 0.0118 |
| 77: PEZZOT | 1.5483 | 0.1569 | 0.0005 | 3.4045 | 0.3415 | 0.0014 |
| 78: PRESCO | 0.8289 | 0.1002 | (0.0759) | 1.9305 | 0.2318 | NS |
| 79: PRESCO | 0.7383 | 0.0942 | NS | 1.6725 | 0.2122 | NS |
| 80: SEGI2 | 0.5679 | 0.0991 | NS | 1.2849 | 0.2208 | NS |
| 81: SEGI2 | 0.1503 | 0.1297 | NS | 0.3513 | 0.2865 | NS |
| 82: SHAW | 1.1326 | 0.1121 | NS | 2.5298 | 0.2509 | NS |
| 83: SOBUE | 0.4048 | 0.0594 | NS | 0.8893 | 0.1309 | NS |
| 84: SPEIZE | 0.8772 | 0.0390 | NS | 1.9509 | 0.0870 | NS |
| 85: STOCKW | 0.8822 | 0.0096 | NS | 1.9383 | 0.0210 | NS |
| 86: SVENSS | 0.9255 | 0.1158 | NS | 2.0479 | 0.2573 | NS |
| 87: TENKAN | 0.6211 | 0.1092 | 0.0001 | 1.4407 | 0.2484 | 0.0003 |
| 88: TSUGAN | 0.1104 | 0.1169 | NS | 0.2461 | 0.2574 | NS |
| 89: TULINI | 1.0019 | 0.0901 | NS | 2.2394 | 0.2008 | NS |
| 90: TULINI | 1.2489 | 0.0862 | (0.0728) | 2.8447 | 0.1983 | 0.0098 |
| 91: TVERDA | 0.6063 | 0.0773 | NS | 1.3657 | 0.1746 | NS |
| 92: TVERDA | 0.9309 | 0.1838 | NS | 2.1244 | 0.4198 | NS |
| 93: WAKAI | 0.6776 | 0.1099 | (0.0831) | 1.5073 | 0.2430 | NS |
| 94: WU | 0.5916 | 0.1017 | NS | 1.3183 | 0.2263 | NS |
| 95: WYNDE6 | 0.9181 | 0.0373 | NS | 2.0237 | 0.0820 | NS |
| 96: WYNDE6 | 0.9796 | 0.0371 | 0.0102 | 2.1767 | 0.0825 | 0.0060 |
| 97: YAMAGU | 0.6608 | 0.1223 | NS | 1.4756 | 0.2723 | NS |

[1]c = cigarettes/d; [2]Not significant (NS) indicates $P \geq 0.1$. $P$ values in the range $0.05 \leq P < 0.1$ are shown in brackets.

**Table 6 Amount smoked by current smokers - inverse-variance weighted simple regression analyses of $\beta_1$ based on best-fitting log + baseline model**

| Factor | Level | *n* | $\beta_1$ (95% CI) | *P*[1] | RR for 20 cigs/d |
|---|---|---|---|---|---|
| All | | 97 | 0.83 (0.80-0.86) | | 10.71 |
| Sex | Male | 55 | 0.79 (0.75-0.84) | < 0.05 | 9.50 |
| | Female | 34 | 0.82 (0.75-0.88) | | 10.21 |
| | Combined | 8 | 0.89 (0.84-0.94) | | 12.50 |
| Study type | Case-control | 49 | 0.86 (0.82-0.90) | < 0.1 | 11.48 |
| | Prospective | 48 | 0.80 (0.76-0.85) | | 9.85 |
| Continent | North America | 43 | 0.87 (0.84-0.89) | < 0.001 | 11.48 |
| | Europe | 32 | 0.83 (0.76-0.90) | | 10.65 |
| | Asia | 17 | 0.53 (0.45-0.61) | | 4.53 |
| | Other | 5 | 0.80 (0.61-0.99) | | 9.80 |
| Publication year[2] | < 1990 | 40 | 0.83 (0.79-0.88) | < 0.1 | 10.71 |
| | 1990-1994 | 29 | 0.77 (0.70-0.84) | | 8.90 |
| | 1995-1999 | 28 | 0.87 (0.82-0.92) | | 11.94 |
| Product[3] | Any product | 20 | 0.75 (0.64-0.85) | NS | 8.36 |
| | Cigarettes +/- | 61 | 0.85 (0.81-0.88) | | 11.09 |
| | Cigarettes only | 16 | 0.82 (0.74-0.90) | | 10.19 |
| Unexposed | Never cigarettes | 32 | 0.83 (0.76-0.90) | NS | 10.49 |
| | Never any product | 65 | 0.84 (0.80-0.87) | | 10.76 |
| Grouped midpoint age (yr) | < 50 | 14 | 0.79 (0.67-0.92) | < 0.1 | 9.57 |
| | 50-59 | 62 | 0.85 (0.82-0.89) | | 11.35 |
| | 60+ | 21 | 0.79 (0.71-0.84) | | 9.13 |
| Cases in smokers | < 100 | 29 | 0.67 (0.56-0.78) | < 0.001 | 6.72 |
| | 100 to < 200 | 28 | 0.73 (0.64-0.83) | | 8.08 |
| | 200 to < 500 | 16 | 0.76 (0.65-0.87) | | 8.72 |
| | 500 to < 1000 | 16 | 0.80 (0.75-0.86) | | 9.87 |
| | 1000+ | 8 | 0.89 (0.85-0.92) | | 12.42 |

[1]Probability values for factor considered, presented as < 0.001, < 0.01, < 0.05, < 0.1 or not significant (NS) ($P \geq 0.1$); [2]Of principal publication for the study; [3]Any product = Smokes cigarettes and/or pipes and/or cigars; Cigarettes +/- = Smokes cigarettes with or without other products (pipes, cigars).

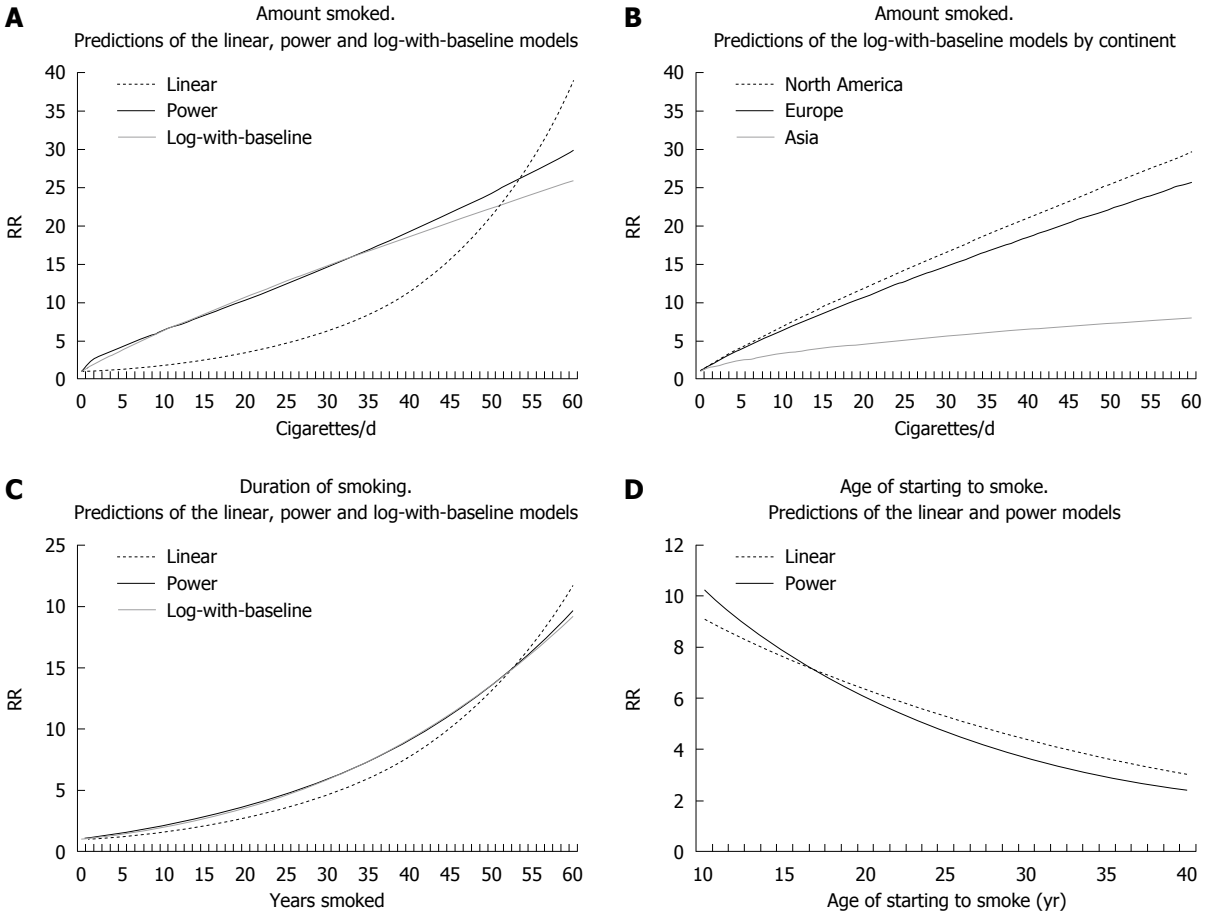


**Figure 1 Model predictions.** A: Amount smoked. Predictions of the linear, power and log-with-baseline models; B: Amount smoked. Predictions of the log-with-baseline models by continent; C: Duration of smoking. Predictions of the linear, power, and log-with-baseline models; D: Age of starting to smoke. Predictions of the linear and power models. The RR is plotted against number of cigarettes per day (A and B), years smoked (C) and age of starting to smoke (D). The linear model for amount smoked is the poorest fit to the data, other models shown fitting the data similarly well.

For the 97 blocks combined the RRs predicted by the log-with-baseline model for 5, 10, 20, 30, 40 and 50 cigs/d are, respectively, 3.86, 6.30, 10.71, 14.77, 18.62 and 22.31. The RRs are similar for the power model (4.30, 6.33, 10.34, 14.61, 19.24 and 24.29), but very different for the linear model (1.36, 1.84, 3.39, 6.25, 11.50 and 21.19). See also Figure 1A which compares model predictions, and Figure 1B which shows the predictions by continent.

### *Duration of smoking*

Blocks[11] gives details of the 35 blocks, derived from 14 studies. CPS I and CPS Ⅱ provide 20 blocks, with data by sex and age. Three further studies provide sex-specific results, the remaining nine only providing one block each. Three studies are from Europe, two South America and one Asia, the remaining eight being from North America.

Table 7 summarizes the dose-response data. A clear increase in risk with increasing duration is evident, 34 blocks (97.1%) showing a greater RR for the longest than the shortest duration group, and 22 (62.9%) showing a strictly monotonic increase in RR.

Table 8 summarizes the analyses on model suitability. The exponential model is again very poor, explaining only 31.47% of the deviance. Other models differ little, explaining 88.49% to 89.96%. The best single parameter models are the best-fitting power model (89.96%) and log-with-baseline model (89.89%).

Fit Duration[11], gives full details for the further analyses using the linear model and best-fitting power and log-with-baseline models, laid out as Fit Amount Smoked[11].

Table 9 compares observed and fitted cases summed over blocks. Misfit is similar for all three models, and significant ($P < 0.001$), though its extent seems relatively moderate.

Table 10 gives fitted values of $\beta_1$ and SE and goodness-of-fit $P$ values for the power and log-with-baseline models. We comment on six blocks where $P$ is $< 0.001$ for both models, and three where $P$ is $< 0.001$ for one model (Fit Duration[11] and Table 7 for further details). In three blocks (1: AMANDU, 29: HUMBLE, 35: PEZZO2) the RR associated with the lowest duration level is large, but the RRs associated with higher levels are not much larger (or even smaller). In another block (10: CPS I males age 65-74 years) the misfit comes from the lack of rise in risk over short duration levels, while in another (17: CPS Ⅱ males age 30-44 years) it is associated with the very high risk for the longest duration. In three other blocks (11: CPS I males age 75+ years, 15: CPS I females age 65-74 years, 20: CPS Ⅱ males age 65-74 years) the misfit is at least partly due to the non-monotonic dose-response.

**Table 7 Duration of smoking by current smokers (yr) - dose-response data**

| Block: Study | Duration of smoking groupings (yr) | Mean values | RRs[1] |
|---|---|---|---|
| 1: AMANDU | 0-24, 25+ | 12.66, 41.28 | 5.92, 7.02 M |
| 2: BEST | 1-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40+ | 2.64, 7.02, 12.03, 16.89, 24.03, 33.93, 51.12 | 1.60, 2.60, 2.30, 3.20, 4.10, 13.90, 14.20 |
| 3: BOUCOT | 1-39, 40+ | 32.05, 51.14 | 42.40, 89.94 M |
| 4: BUFFLE | 1-30, 31-40, 41+ | 19.34, 35.56, 48.49 | 14.00, 14.70, 18.15 M |
| 5: CEDERL | 1-29, 30+ | 23.94, 41.09 | 1.80, 7.40 M |
| 6: CEDERL | 1-29, 30+ | 22.26, 39.47 | 1.60, 9.60 M |
| 7: CPS I | 1-29, 30+ | 23.70, 32.03 | 3.83, 6.56 M |
| 8: CPS I | 1-29, 30-34, 35-39, 40+ | 24.92, 31.91, 36.52, 43.07 | 5.58, 13.40, 16.93, 29.61 M |
| 9: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50+ | 23.57, 32.25, 37.75, 42.03, 46.80, 51.81 | 3.11, 6.57, 10.35, 15.21, 21.46, 33.11 M |
| 10: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60+ | 10.67, 30.00, 39.00, 42.21, 47.57, 52.05, 56.73, 62.87 | 5.46, 6.26, 5.86, 8.22, 12.48, 15.28, 18.86, 28.60 |
| 11: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60+ | 20.00, 32.00, 37.00, 41.00, 46.25, 51.86, 57.00, 65.03 | 2.17, 2.27, 12.66, 3.47, 6.22, 6.31, 12.87, 13.23 |
| 12: CPS I | 1-29, 30+ | 21.86, 31.37 | 6.16, 13.80 M |
| 13: CPS I | 1-29, 30-34, 35-39, 40+ | 23.29, 31.61, 36.72, 43.09 | 2.90, 6.91, 8.49, 19.48 M |
| 14: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50+ | 21.03, 31.92, 37.45, 42.21, 46.65, 52.80 | 1.51, 3.71, 4.73, 5.72, 7.78, 14.48 M |
| 15: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55+ | 21.69, 31.38, 37.19, 41.80, 47.14, 51.76, 57.56 | 2.30, 3.38, 3.67, 5.81, 7.01, 6.20, 3.32 |
| 16: CPS I | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55+ | 18.00, 30.00, 38.00, 41.75, 46.71, 52.25, 61.54 | 0.38, 3.11, 2.72, 3.22, 1.15, 1.85, 3.20 |
| 17: CPS II | 1-29, 30+ | 19.15, 32.13 | 3.69, 108.27 M |
| 18: CPS II | 1-29, 30-34, 35-39, 40+ | 24.92, 31.91, 36.52, 43.07 | 7.72, 19.47, 25.01, 36.98 M |
| 19: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50+ | 23.57, 32.25, 37.75, 42.03, 46.80, 51.81 | 15.51, 17.86, 27.31, 44.71, 50.92, 72.07 M |
| 20: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60+ | 10.67, 30.00, 39.00, 42.21, 47.57, 52.05, 56.73, 62.87 | 9.97, 11.05, 20.45, 18.59, 24.33, 32.06, 40.43, 45.64 |
| 21: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60+ | 20.00, 32.00, 37.00, 41.00, 46.25, 51.86, 57.00, 66.09 | 7.54, 4.53, 4.37, 16.30, 16.01, 13.40, 18.09, 21.79 |
| 22: CPS II | 1-19, 20+ | 13.93, 24.23 | 10.98, 8.38 |
| 23: CPS II | 1-29, 30-34, 35+ | 23.29, 31.61, 37.81 | 8.96, 18.34, 23.32 M |
| 24: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50+ | 21.03, 31.92, 37.45, 42.22, 46.65, 52.80 | 6.50, 13.04, 17.07, 20.56, 23.94, 28.45 M |
| 25: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55+ | 21.69, 31.38, 37.19, 41.80, 47.14, 51.76, 57.56 | 6.64, 5.57, 10.19, 12.96, 15.79, 18.75, 19.34 |
| 26: CPS II | 1-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60+ | 18.00, 30.00, 38.00, 42.20, 46.71, 52.23, 57.10, 65.06 | 3.36, 7.92, 6.31, 8.14, 11.68, 9.45, 9.18, 19.88 |
| 27: DEAN2 | 1-19, 20+ | 15.09, 38.28 | 3.21, 3.84 M |
| 28: DEAN2 | 1-19, 20+ | 13.93, 35.85 | 0.98, 5.88 |
| 29: HUMBLE | 1-29, 30-39, 40-49, 50+ | 17.18, 34.07, 44.43, 56.60 | 15.45, 17.54, 19.61, 17.27 |
| 30: KAISE2 | 1-39, 40+ | 23.76, 51.12 | 4.86, 15.64 M |
| 31: KAISE2 | 1-39, 40+ | 22.73, 48.96 | 9.09, 30.41 M |
| 32: KATSOU | 1-29, 30+ | 14.58, 42.43 | 1.29, 7.43 M |
| 33: LIAW | 1-20, 21-30, 31+ | 14.32, 26.18, 44.79 | 0.90, 2.60, 4.70 |
| 34: MATOS | 1-24, 25-39, 40+ | 12.75, 31.16, 50.57 | 5.20, 7.40, 10.20 M |
| 35: PEZZO2 | 1-35, 36+ | 17.15, 48.89 | 16.25, 26.77 M |

[1]M indicates a strictly monotonic rise in RR with increasing duration of smoking.

In the remaining block (9: CPS I males age 55-64 years) the rise is monotonic, but the relatively small RR for the shortest duration does not fit in well with the large RRs for longer durations.

Table 11 presents results of weighted simple regression analysis of $\beta_1$ for the power model. Significance at $P < 0.05$ is only seen for midpoint age, with higher $\beta_1$ values for lower ages. In forward stepwise regressions (not shown), the model included in succession midpoint age ($P < 0.05$), number of cases in smokers ($P < 0.05$), smoking product ($P < 0.05$) and unexposed group ($P < 0.01$). The final model associated increased risk with younger age, larger numbers of cases, smoking of cigarettes only or cigarettes ± other products (compared to smoking any product) and with the unexposed being never any product (rather than never cigarettes).

For the 35 blocks combined the RRs predicted by the power model for durations of 10, 20, 30, 40 and 50 years are, respectively, 2.21, 3.75, 5.96, 9.11 and 13.54. Figure 1C compares model predictions.

### Age of starting to smoke

Blocks[11] gives details of the 27 blocks, deriving from 15 studies. One study gives results by age and sex, two by age for males, and five by sex but not age, the remaining seven studies only providing one block each. There are similar numbers of blocks from North America (9), Europe (9) and Asia (8), only one being from elsewhere.

Table 12 summarizes the dose-response data. A relationship of risk to age of starting is not consistently seen. While 13 blocks (48.1%) show a strictly monotonic decline in risk as starting age increases, with risk often substantially higher in early starters, and 6 (22.2%) blocks show a similar non-monotonic tendency, 8 (29.6%) blocks (1, 2, 7-9, 16, 20, 21) show no such tendency.

Table 13 summarizes the analyses on model suitability,

**Table 8 Comparing the suitability of different models relating log RR to duration of smoking by current smokers, expressed as d = years smoked/10**

| Model | Parameter value[1] | Fitted coefficient(s) (SE) | Deviance | DF | Deviance explained (%) |
|---|---|---|---|---|---|
| Null | - | - | 6161.11 | 35 | |
| Linear: log RR = $\beta_1 d$ | - | $\beta_1$ = 0.5134 (0.0069) | 672.01 | 34 | 89.09 |
| Quadratic: log RR = $\beta_1 d + \beta_2 d^2$ | - | $\beta_1$ = 0.6718 (0.0237), $\beta_2$ = -0.0300 (0.0043) | 623.20 | 33 | 89.88 |
| Cubic: log RR = $\beta_1 d + \beta_2 d^2 + \beta_3 d^3$ | - | $\beta_1$ = 0.6788 (0.0607), $\beta_2$ = -0.0330 (0.0243), $\beta_3$ = 0.0003 (0.0025) | 623.19 | 32 | 89.89 |
| Power: log RR = $\beta_1 d^Y$ | Y = 0.50 | $\beta_1$ = 1.1576 (0.0156) | 682.56 | 34 | |
| | Y = 0.72 | $\beta_1$ = 0.8180 (0.0110) | 619.30 | 34 | |
| | Y = 0.73 | $\beta_1$ = 0.8049 (0.0108) | 618.93 | 34 | |
| | Y = 0.74 | $\beta_1$ = 0.7919 (0.0106) | 618.75 | 34 | 89.96 |
| | Y = 0.75 | $\beta_1$ = 0.7791 (0.0105) | 618.76 | 34 | |
| | Y = 0.76 | $\beta_1$ = 0.7665 (0.0103) | 618.95 | 34 | |
| | Y = 1.00 | $\beta_1$ = 0.5134 (0.0069) | 672.01 | 34 | |
| | Y = 2.00 | $\beta_1$ = 0.0863 (0.0013) | 1426.44 | 34 | |
| Log: log RR = $\beta_1 \log d$ | - | $\beta_1$ = 1.5870 (0.0215) | 708.96 | 35 | 88.49 |
| Exponential: log RR = $\beta_1 \exp d$ | | $\beta_1$ = 0.0045 (0.0001) | 4222.01 | 35 | 31.47 |
| Log-with-baseline: log RR = $\beta_1 \log (1 + Wd)$ | W = 0.10 | $\beta_1$ = 6.4054 (0.0861) | 629.58 | 34 | |
| | W = 0.15 | $\beta_1$ = 4.6503 (0.0625) | 623.99 | 34 | |
| | W = 0.18 | $\beta_1$ = 4.0572 (0.0545) | 622.82 | 34 | |
| | W = 0.19 | $\beta_1$ = 3.9001 (0.0524) | 622.69 | 34 | |
| | W = 0.20 | $\beta_1$ = 3.7581 (0.0505) | 622.67 | 34 | 89.89 |
| | W = 0.21 | $\beta_1$ = 3.6293 (0.0488) | 622.74 | 34 | |
| | W = 0.22 | $\beta_1$ = 3.5117 (0.0472) | 622.89 | 34 | |

[1]Note that we only sought the best-fitting value of W and Y to two decimal places.

**Table 9 Duration of smoking by current smokers - observed and fitted lung cancers for the linear, best power and best log-with-baseline model, with $\beta_1$ fitted separately for each block**

| Midpoint years smoked | Observed[1] | Fitted[2] | | |
|---|---|---|---|---|
| | | Linear model | Best power model | Best log-with-baseline model |
| < 15 | 109.36 | 89.10 | 93.61 | 91.19 |
| 15 to < 30 | 605.64 | 584.79 | 666.12 | 645.42 |
| 30 to < 45 | 3968.47 | 3917.11 | 4000.71 | 4012.22 |
| 45+ | 3493.56 | 3573.95 | 3499.85 | 3499.95 |
| Never smoked | 2533.97 | 2546.03 | 2450.69 | 2462.20 |
| Total | 10710.98 | 10710.98 | 10710.98 | 10710.98 |
| Fit statistic[3] | | 28.14 | 25.70 | 24.53 |

[1]Observed pseudo-number of lung cancer cases, summed over blocks; [2]Fitted pseudo-number of lung cancer cases, summed over blocks. For each study, the fitted number of cases for each block is calculated from the numbers at risk and the fitted RRs by years smoked, derived from the fitted value of $\beta_1$; [3]Based on summation of (observed-fitted)$^2$/fitted, the summation also including terms for the observed and fitted total numbers of controls (not shown). The statistic can be considered to be approximately chisquared distributed on 6 df, and is significant at $P < 0.001$ for all three models.

taking (70-age at starting) as a duration-like measure. The exponential model again is the poorest, explaining only 60.24% of the deviance, and the log model is also poorer than the other models. Although slightly more deviance is explained by the cubic model, the best-fitting power model is the best simple model, explaining 88.29% of the deviance. Log-with-baseline models were also tried (not shown), but the best-fitting value of W was extremely low, so it became essentially identical to the linear model, having the same deviance.

Fit Age Start[11], gives full details of the further analyses using the linear and best-fitting power models.

Table 14 compares observed and fitted cases summed over blocks. Both the linear and best-fitted power models fit well.

Table 15 gives fitted values of $\beta_1$ and SE and goodness-of-fit *P* values. For no block does either model show misfit at $P < 0.01$, though misfits at $P < 0.05$ are sometimes seen. We comment on four blocks with some evidence ($P < 0.1$) of misfit to both models (Table 12 and Fit Age Start[11] for further details). For block 4 (CPS I males aged 55-69) the misfit seems due to the relatively small decline in risk between age of start 1-14 and 15-19 years, compared to a greater decline subsequently. For block 5 (CPS I males aged 70-84 years), risk again declines substantially over ages of start 15-19, 20-24 and 25+ years, but risk is slightly less at age 1-14 than 15-19 years. For block 12 (ENGELA males), risk decreases from age 1-19 to 20-29 years but then falls no further. For block 17 (LIAW), the pattern is non-monotonic.

Table 16 presents results of the weighted simple regression analyses of $\beta_1$ for the power model. Various fac-

**Table 10 Duration of smoking by current smokers - fitted values for of β1 and SE, and *P* values for goodness-of-fit tests for the best-fitting power model and log-with-baseline model**

| Block: Study | Log-with-baseline model[1] log RR = β1 [1 + (0.2 yr/10)] | | | Power model[1] log RR = β1 (yr/10)$^{0.74}$ | | |
|---|---|---|---|---|---|---|
| | β1 | SE β1 | *P* (fit)[2] | β1 | SE β1 | *P* (fit)[2] |
| 1: AMANDU | 1.5114 | 0.5504 | 0.0030 | 0.3454 | 0.1210 | 0.0046 |
| 2: BEST | 3.7163 | 0.4210 | (0.0548) | 0.7995 | 0.0908 | 0.0469 |
| 3: BOUCOT | 6.7731 | 1.6574 | NS | 1.4235 | 0.3482 | NS |
| 4: BUFFLE | 4.5141 | 0.4888 | 0.0466 | 0.9570 | 0.1029 | (0.0780) |
| 5: CEDERL | 3.4044 | 0.7166 | NS | 0.7147 | 0.1512 | NS |
| 6: CEDERL | 3.3566 | 0.7692 | NS | 0.6990 | 0.1609 | NS |
| 7: CPS I | 3.6386 | 1.4531 | NS | 0.7530 | 0.3009 | NS |
| 8: CPS I | 5.7248 | 0.4753 | (0.0947) | 1.2122 | 0.1011 | (0.0518) |
| 9: CPS I | 4.8058 | 0.2032 | 0.0003 | 1.0130 | 0.0429 | 0.0002 |
| 10: CPS I | 3.7681 | 0.1557 | 0.0002 | 0.7976 | 0.0328 | 0.0010 |
| 11: CPS I | 3.1437 | 0.1768 | 0.0079 | 0.6566 | 0.0369 | 0.0073 |
| 12: CPS I | 5.1328 | 1.5211 | NS | 1.0518 | 0.3119 | NS |
| 13: CPS I | 3.9960 | 0.3377 | 0.0308 | 0.8342 | 0.0708 | 0.0165 |
| 14: CPS I | 2.8575 | 0.1844 | (0.0637) | 0.5999 | 0.0388 | 0.0383 |
| 15: CPS I | 2.6384 | 0.1872 | 0.0000 | 0.5544 | 0.0394 | 0.0000 |
| 16: CPS I | 1.5443 | 0.3346 | NS | 0.3238 | 0.0702 | NS |
| 17: CPS II | 9.5482 | 2.4662 | 0.0149 | 1.9485 | 0.5160 | 0.0076 |
| 18: CPS II | 6.1160 | 0.5675 | NS | 1.2874 | 0.1199 | NS |
| 19: CPS II | 5.9905 | 0.3222 | (0.0749) | 1.2722 | 0.0684 | (0.0921) |
| 20: CPS II | 4.5913 | 0.1996 | 0.0058 | 0.9714 | 0.0421 | 0.0210 |
| 21: CPS II | 3.6604 | 0.2069 | NS | 0.7645 | 0.0432 | NS |
| 22: CPS II | 5.1073 | 3.0925 | NS | 1.1011 | 0.6362 | NS |
| 23: CPS II | 5.8103 | 0.4709 | NS | 1.2180 | 0.0988 | NS |
| 24: CPS II | 4.9498 | 0.2256 | NS | 1.0461 | 0.0476 | NS |
| 25: CPS II | 4.1028 | 0.1646 | NS | 0.8656 | 0.0347 | NS |
| 26: CPS II | 3.3310 | 0.1915 | NS | 0.6993 | 0.0402 | NS |
| 27: DEAN2 | 2.1038 | 0.3399 | NS | 0.4515 | 0.0723 | NS |
| 28: DEAN2 | 2.9155 | 0.6412 | NS | 0.5984 | 0.1334 | NS |
| 29: HUMBLE | 4.2780 | 0.2807 | 0.0091 | 0.9005 | 0.0590 | 0.0148 |
| 30: KAISE2 | 3.8758 | 0.4357 | NS | 0.8202 | 0.0922 | NS |
| 31: KAISE2 | 4.7883 | 0.5320 | NS | 1.0198 | 0.1130 | NS |
| 32: KATSOU | 2.9305 | 0.7339 | NS | 0.6031 | 0.1527 | NS |
| 33: LIAW | 2.4277 | 0.4372 | NS | 0.5093 | 0.0921 | NS |
| 34: MATOS | 3.4356 | 0.5336 | NS | 0.7276 | 0.1124 | NS |
| 35: PEZZO2 | 3.3022 | 0.5283 | 0.0002 | 0.7260 | 0.1137 | 0.0005 |

[1]Years smoked; [2]Not significant (NS) indicates $P \geq 0.1$. *P* values in the range $0.05 \leq P < 0.1$ are shown in brackets.

tors are significant at $P < 0.05$, including number of lung cancer cases ($P < 0.001$), continent ($P < 0.01$), publication year ($P < 0.01$), sex ($P < 0.05$) and product smoked ($P < 0.05$), though in a forward stepwise model (details not shown), only two factors were included: number of lung cancer cases ($P < 0.001$) and midpoint age ($P < 0.05$). However, the relationship of β1 to number of cases was not smooth (higher risks for 100 to < 200, and 500 to < 1000 cases and lower risks for < 100, 200 to < 500 and 1000+) so the result is difficult to interpret. The association with age is related to a lower β1 in older subjects (aged 60+ years).

For the 31 blocks combined, the RRs predicted for age of start 12.5, 15, 17.5, 20, 25 and 30 years are, respectively, 8.94, 7.80, 6.83, 5.99, 4.66 and 3.66 for the power model and 8.31, 7.57, 6.91, 6.30, 5.24 and 4.36 for the linear model (Figure 1D).

## DISCUSSION

In our earlier review[1] of the evidence relating smoking to lung cancer, we demonstrated a clear dose-response with the three measures considered, risk increasing with increasing amount smoked and duration and with decreasing age of starting. We extend this work by fitting parametric models to the dose-relationships.

We tried various models. The most useful were the "linear model" (log RR = $\beta_1 d$), the "power model" (log RR = $\beta_1 d^Y$) and the "log-with-baseline model" [log RR = $\beta_1 \log (1 + Wd)$], where d is dose. For amount smoked, the linear model proved inadequate, but a reasonable fit was found with the other two models, the best fit being for the log-with-baseline model with W = 0.81. For duration, all three models were reasonable, the best being the power model with Y = 0.74. For age of starting, where we used a duration-like dose measure based on (70 - age of starting to smoke), the best-fitting model was again the power model, here with Y = 1.44.

Inverse-variance weighted analyses were also carried out to identify sources of heterogeneity in β1. For amount smoked, as expected from our earlier review[1], the major source was continent, the fitted slope being much less

**Table 11 Duration of smoking by current smokers - inverse-variance weighted simple regression analyses of β1 based on best-fitting power model**

| Factor | Level | *n* | β1 (95%CI) | *P*[1] | RR for 30 yr smoked |
|---|---|---|---|---|---|
| All | | 35 | 0.79 (0.72-0.86) | | 5.94 |
| Sex | Male | 18 | 0.84 (0.73-0.94) | NS | 6.59 |
| | Female | 15 | 0.74 (0.64-0.85) | | 5.35 |
| | Combined | 2 | 0.79 (0.45-1.12) | | 5.89 |
| Study type | Case-control | 7 | 0.73 (0.50-0.97) | NS | 5.24 |
| | Prospective | 28 | 0.80 (0.72-0.87) | | 6.02 |
| Continent | North America | 27 | 0.81 (0.73-0.88) | NS | 6.19 |
| | Europe | 5 | 0.55 (0.20-0.90) | | 3.44 |
| | Asia | 1 | 0.51 (-0.11-1.13) | | 3.15 |
| | Other | 2 | 0.73 (0.19-1.27) | | 5.15 |
| Publication year[2] | < 1990 | 8 | 0.76 (0.52-0.99) | NS | 5.50 |
| | 1990-1994 | 2 | 0.44 (-0.20-1.09) | | 2.73 |
| | 1995-1999 | 25 | 0.80 (0.72-0.88) | | 6.08 |
| Product[3] | Any product | 4 | 0.50 (0.18-0.83) | NS | 3.12 |
| | Cigarettes +/- | 10 | 0.86 (0.73-0.98) | | 6.89 |
| | Cigarettes only | 21 | 0.78 (0.70-0.87) | | 5.85 |
| Unexposed | Never cigarettes | 19 | 0.77 (0.69-0.86) | NS | 5.71 |
| | Never any product | 16 | 0.85 (0.71-0.99) | | 6.75 |
| Grouped midpoint age (yr) | < 50 | 8 | 1.06 (0.78-1.34) | < 0.05 | 11.00 |
| | 50-59 | 13 | 0.87 (0.75-0.99) | | 7.04 |
| | 60+ | 14 | 0.73 (0.65-0.82) | | 5.21 |
| Cases in smokers | < 100 | 14 | 0.62 (0.39-0.84) | NS | 4.01 |
| | 100 to < 200 | 9 | 0.73 (0.59-0.87) | | 5.19 |
| | 200 to < 500 | 6 | 0.78 (0.67-0.89) | | 5.18 |
| | 500 to < 1000 | 5 | 0.95 (0.80-1.10) | | 8.58 |
| | 1000+ | 1 | 0.80 (0.59-1.01) | | 6.04 |

[1]Probability values for factor considered, presented as < 0.001, < 0.01, < 0.05, < 0.1 or not significant (NS) ($P \geqslant 0.1$); [2]Of principal publication for the study; [3]Any product = Smokes cigarettes and/or pipes and/or cigars; Cigarettes +/- = Smokes cigarettes with or without other products (pipes, cigars).

**Table 12 Age of starting to smoke by current smokers (yr) - dose-response data**

| Block: Study | Age of starting to smoke groupings (yr) | Mean values | RRs[1] |
|---|---|---|---|
| 1: CEDERL | < 17, 17-18, 19+ | 13.83, 17.52, 22.45 | 6.40, 9.80, 6.50 |
| 2: CEDERL | < 17, 17-18, 19+ | 14.31, 17.56, 24.32 | 0.61, 1.84, 1.99 |
| 3: CPS I | < 15, 15-19, 20-24, 25+ | 11.98, 16.74, 21.29, 28.47 | 15.00, 9.71, 7.14, 3.43 M |
| 4: CPS I | < 15, 15-19, 20-24, 25+ | 11.59, 16.56, 21.00, 30.90 | 18.16, 16.32, 12.00, 5.21 M |
| 5: CPS I | < 15, 15-19, 20-24, 25+ | 11.19, 16.61, 21.07, 35.00 | 14.03, 16.60, 8.66, 1.71 |
| 6: CPS I | < 15, 15-19, 20-24, 25+ | 12.71, 16.88, 21.26, 31.51 | 9.00, 5.00, 4.00, 1.50 M |
| 7: CPS I | < 20, 20-24, 25+ | 16.02, 20.95, 33.29 | 2.59, 3.23, 2.62 |
| 8: DEAN3 | < 15, 15-19, 20-24, 25+ | 11.73, 16.67, 21.19, 29.95 | 5.67, 7.01, 6.86, 6.80 |
| 9: DEAN3 | < 15, 15-19, 20-24, 25+ | 12.45, 16.95, 21.15, 32.19 | 2.41, 2.90, 2.95, 3.70 |
| 10: DORN | < 15, 15-19, 20-24, 25+ | 11.63, 16.43, 21.23, 30.88 | 23.42, 16.25, 11.06, 5.18 M |
| 11: DORN | < 15, 15-19, 20-24, 25+ | 11.37, 16.81, 20.69, 32.63 | 14.18, 11.31, 7.94, 4.95 M |
| 12: ENGELA | < 20, 20-29, 30+ | 15.08, 22.23, 35.10 | 7.42, 3.60, 3.79 |
| 13: ENGELA | < 20, 20-29, 30+ | 15.80, 22.63, 35,80 | 11.29, 8.15, 2.73 M |
| 14: GAO2 | < 20, 20-29, 30+ | 15.11, 22.17, 35.94 | 8.62, 6.44, 2.15 M |
| 15: HIRAYA | < 20, 20+ | 14.90, 24.02 | 5.71, 4.35 M |
| 16: HIRAYA | < 20, 20+ | 15.87, 27.40 | 0.78, 2.46 |
| 17: LIAW | < 21, 21-24, 25+ | 15.70, 21.94, 32.03 | 4.60, 5.90, 1.50 |
| 18: MATOS | < 15, 15-19, 20+ | 11.96, 16.64, 23.49 | 11.30, 8.60, 5.30 M |
| 19: MIGRAN | < 16, 16-19, 20+ | 12.60, 17.19, 23.71 | 10.03, 6.93, 7.79 |
| 20: MIGRAN | < 16, 16-19, 20+ | 12.94, 17.31, 26.17 | 7.17, 8.29, 7.98 |
| 21: MRFITR | < 16, 16-17, 18-19, 20-21, 22-23, 24+ | 12.93, 16.45, 18.31, 20.40, 22.35, 27.74 | 45.91, 67.17, 50.54, 27.09, 60.06, 23.91 |
| 22: SEGI2 | < 20, 20-22, 23+ | 15.28, 20.77, 26.60 | 8.21, 5.56, 1.83 M |
| 23: SEGI2 | < 20, 20-22, 23+ | 14.87, 20.90, 28.96 | 8.70, 5.68, 3.56 M |
| 24: SEGI2 | < 20, 20-22, 23+ | 14.37, 20.59, 30.87 | 3.26, 1.70, 1.52 M |
| 25: SVENSS | < 19, 19-25, 26+ | 15.04, 21.31, 33.89 | 7.82, 13.08, 5.61 |
| 26: WAKAI | < 20, 20-29, 30+ | 14.91, 22.14, 37.23 | 3.69, 4.62, 2.08 |
| 27: WU | < 19, 19-24, 25+ | 15.06, 20.71, 31.44 | 10.32, 3.57, 1.55 M |

[1]M indicates a strictly monotonic decline in RR with increasing age of starting to smoke.

**Table 13 Comparing the suitability of different models relating log *RR* to age of starting smoke by current smokers, expressed as d = (70-age at start)/10**

| Model | Parameter value[1] | Fitted coefficient(s) (SE) | Deviance | DF | Deviance explained (%) |
|---|---|---|---|---|---|
| Null | - | - | 2145.30 | 27 | |
| Linear: log RR = $\beta_1 d$ | - | $\beta_1$ = 0.3681 (0.0085) | 276.67 | 26 | 87.10 |
| Quadratic: log RR = $\beta_1 d + \beta_2 d^2$ | - | $\beta_1$ = 0.1987 (0.0349)<br>$\beta_2$ = 0.0318 (0.0064) | 251.63 | 25 | 88.27 |
| Cubic: log RR = $\beta_1 d + \beta_2 d^2 + \beta_3 d^3$ | - | $\beta_1$ = -0.0415 (0.2143)<br>$\beta_2$ = 0.1304 (0.0870)<br>$\beta_3$ = -0.0100 (0.0088) | 250.34 | 24 | 88.33 |
| Power: log RR = $\beta_1 d^Y$ | Y = 0.75 | $\beta_1$ = 0.5515 (0.0129) | 316.69 | 26 | |
| | Y = 1.00 | $\beta_1$ = 0.3681 (0.0085) | 276.67 | 26 | |
| | Y = 1.42 | $\beta_1$ = 0.1825 (0.0042) | 251.27 | 26 | |
| | Y = 1.43 | $\beta_1$ = 0.1794 (0.0041) | 251.24 | 26 | |
| | Y = 1.44 | $\beta_1$ = 0.1764 (0.0041) | 251.23 | 26 | 88.29 |
| | Y = 1.45 | $\beta_1$ = 0.1734 (0.0040) | 251.25 | 26 | |
| | Y = 1.46 | $\beta_1$ = 0.1705 (0.0039) | 251.28 | 26 | |
| | Y = 1.50 | $\beta_1$ = 0.1592 (0.0037) | 251.67 | 26 | |
| | Y = 2.00 | $\beta_1$ = 0.0668 (0.0015) | 284.04 | 26 | |
| Log: log RR = $\beta_1 \log d$ | - | $\beta_1$ = 1.1460 (0.0270) | 340.23 | 26 | 84.14 |
| Exponential: log RR = $\beta_1 \exp d$ | - | $\beta_1$ = 0.0058 (0.0002) | 852.85 | 26 | 60.24 |

[1]Note that we only sought the best-fitting value of Y to two decimal places.

**Table 14 Age of starting to smoke by current smokers - observed and fitted lung cancers for the linear and best power model, with $\beta_1$ fitted separately for each block**

| Age of starting (yr) | Observed[1] | Fitted[2] | |
|---|---|---|---|
| | | Linear model | Best power model |
| < 16 | 1304.92 | 1294.48 | 1387.73 |
| 16 to < 20 | 1964.76 | 1906.55 | 1921.20 |
| 20 to < 24 | 1227.48 | 1266.99 | 1216.48 |
| 25+ | 2173.90 | 2219.26 | 2122.14 |
| Never smoked | 894.41 | 878.20 | 917.92 |
| Total | 7565.47 | 7565.47 | 7565.47 |
| Fit statistic[3] | | 4.77 | 9.75 |

[1]Observed pseudo-number of lung cancer cases, summed over blocks; [2]Fitted pseudo-number of lung cancer cases, summed over blocks. For each study, the fitted number of cases for each block is calculated from the numbers at risk and the fitted relative risks for age of starting to smoke, derived from the fitted value of $\beta_1$; [3]Based on summation of (observed-fitted)$^2$/fitted, the summation also including terms for the observed and fitted total numbers of controls (not shown). The statistic can be considered to be approximately chisquared distributed on 6 df and is not significant ($P > 0.1$) for both models.

steep for Asian than European or North American studies. However, it proved more difficult to identify meaningful major sources for the other measures.

We discuss various issues relating to interpretation of these findings.

### Adequacy of literature search and publication bias

All the data used came from the IESLC database. The source paper[1] demonstrated that the search was comprehensive, though limited to papers published before 2000 and studies of 100+ cases. Publication bias was discussed earlier[1], evidence for its existence being considered not strong. The probability of dose-response results being published might depend on the strength of the overall relationship seen. While clearly demonstrated for passive smoking and lung cancer[3], this seems less relevant here, the association with active smoking being so strong. Nevertheless, some publication bias may exist.

There are various reasons why the fitted dose-relationships may not accurately reflect the true relationships.

### Misclassification of smoking status

It is well-documented (*e.g.*,[12,13]) that some subjects deny current or past smoking, so increasing the apparent lung cancer risk in reported never smokers and biasing downwards the estimated smoking RR. Such misclassification is difficult to adjust for, as it varies by aspects of study design, the questions asked, and also by sex, age, location and other demographics. Indeed, higher denial rates in Asian populations[14] may contribute to the markedly weaker observed associations seen in Asia.

In prospective studies there is an additional problem, especially in studies with long-term follow-up with no re-interviews to update smoking status. In particular, some subjects classified at baseline as current smokers may quit during follow-up. Also some never smokers may start, though this is less likely given the subjects' age at baseline in many studies.

### Misclassification of amount smoked

Similar problems arise. Subjects may understate (or overstate) the amount they smoke, and during follow-up in prospective studies, may reduce or increase the amount smoked. Although some studies, particularly case-control, may ask questions on habits at various times during the subject's smoking career, the data reported may relate to average consumption. Someone smoking, say, 30 cigarettes/d for 20 years, then 10 cigarettes/d for 20 years, may not have the same risk as someone smoking 20 cigarettes/d for the whole 40 years period. Difficulties in re-

**Table 15 Age of starting to smoke by current smokers - fitted values of $\beta_1$ and SE, and *P* values for goodness-of-fit tests for the linear model and for the best-fitting power model**

| Block: Study | Linear model[1] log RR = $\beta_1$(70 - a)/10 | | | Power model[1] log RR = $\beta_1$(70 - a)/$10^{1.44}$ | | |
|---|---|---|---|---|---|---|
| | $\beta_1$ | SE $\beta_1$ | *P* (fit)[2] | $\beta_1$ | SE $\beta_1$ | *P* (fit)[2] |
| 1: CEDERL | 0.0385 | 0.0082 | NS | 0.1828 | 0.0394 | NS |
| 2: CEDERL | 0.0140 | 0.0089 | NS | 0.0699 | 0.0445 | NS |
| 3: CPS I | 0.0461 | 0.0041 | 0.0490 | 0.2167 | 0.0188 | NS |
| 4: CPS I | 0.0524 | 0.0029 | (0.0959) | 0.2399 | 0.0135 | (0.0579) |
| 5: CPS I | 0.0512 | 0.0047 | 0.0195 | 0.2408 | 0.0223 | 0.0307 |
| 6: CPS I | 0.0301 | 0.0036 | (0.0510) | 0.1480 | 0.0175 | NS |
| 7: CPS I | 0.0237 | 0.0046 | NS | 0.1168 | 0.0238 | 0.0828 |
| 8: DEAN3 | 0.0332 | 0.0041 | NS | 0.1482 | 0.0189 | 0.0342 |
| 9: DEAN3 | 0.0209 | 0.0039 | NS | 0.0960 | 0.0187 | NS |
| 10: DORN | 0.0549 | 0.0037 | (0.0874) | 0.2527 | 0.0166 | NS |
| 11: DORN | 0.0455 | 0.0027 | NS | 0.2086 | 0.0125 | NS |
| 12: ENGELA | 0.0360 | 0.0037 | 0.0109 | 0.1682 | 0.0171 | 0.0269 |
| 13: ENGELA | 0.0442 | 0.0045 | NS | 0.2186 | 0.0221 | NS |
| 14: GAO2 | 0.0394 | 0.0066 | NS | 0.1909 | 0.0318 | NS |
| 15: HIRAYA | 0.0317 | 0.0022 | NS | 0.1497 | 0.0104 | 0.0288 |
| 16: HIRAYA | 0.0207 | 0.0029 | NS | 0.1086 | 0.0152 | NS |
| 17: LIAW | 0.0296 | 0.0050 | 0.0396 | 0.1448 | 0.0242 | (0.0661) |
| 18: MATOS | 0.0411 | 0.0063 | NS | 0.1933 | 0.0296 | NS |
| 19: MIGRAN | 0.0373 | 0.0087 | NS | 0.1612 | 0.0385 | NS |
| 20: MIGRAN | 0.0400 | 0.0108 | NS | 0.1859 | 0.0519 | NS |
| 21: MRFITR | 0.0686 | 0.0237 | NS | 0.2931 | 0.1055 | NS |
| 22: SEGI2 | 0.0468 | 0.0140 | NS | 0.2325 | 0.0639 | NS |
| 23: SEGI2 | 0.0440 | 0.0128 | NS | 0.1974 | 0.0557 | NS |
| 24: SEGI2 | 0.0192 | 0.0109 | NS | 0.0945 | 0.0500 | NS |
| 25: SVENSS | 0.0432 | 0.0051 | NS | 0.2064 | 0.0246 | NS |
| 26: WAKAI | 0.0275 | 0.0068 | NS | 0.1244 | 0.0318 | NS |
| 27: WU | 0.0348 | 0.0063 | NS | 0.1741 | 0.0305 | NS |

[1]a = Age of starting to smoke; [2]Not significant (NS) indicates $P \geqslant 0.1$. *P* values in the range $0.05 \leqslant P < 0.1$ are shown in brackets.

**Table 16 Age of starting to smoke by current smokers - inverse-variance weighted simple regression analyses of $\beta_1$ based on best-fitting power model**

| Factor | Level | *n* | $\beta_1$ (95%CI) | *P*[1] | RR for 15 yr start |
|---|---|---|---|---|---|
| All | | 27 | 0.18 (0.16-0.20) | | 7.80 |
| Sex | Male | 17 | 0.19 (0.17-0.21) | < 0.05 | 9.49 |
| | Female | 9 | 0.14 (0.11-0.17) | | 5.14 |
| | Combined | 1 | 0.14 (0.04-0.25) | | 5.40 |
| Study type | Case-control | 10 | 0.15 (0.11-0.20) | NS | 5.94 |
| | Prospective | 17 | 0.18 (0.16-0.20) | | 8.37 |
| Continent | North America | 9 | 0.21 (0.19-0.23) | < 0.01 | 11.49 |
| | Europe | 9 | 0.16 (0.13-0.19) | | 6.38 |
| | Asia | 8 | 0.14 (0.11-0.17) | | 5.17 |
| | Other | 1 | 0.19 (0.08-0.31) | | 9.50 |
| Publication year[2] | < 1990 | 11 | 0.15 (0.11-0.19) | < 0.01 | 5.59 |
| | 1990-1994 | 4 | 0.14 (0.11-0.17) | | 5.17 |
| | 1995-1999 | 12 | 0.20 (0.18-0.22) | | 10.37 |
| Product[3] | Any product | 3 | 0.17 (0.11-0.24) | < 0.05 | 7.65 |
| | Cigarettes +/- | 16 | 0.19 (0.17-0.21) | | 9.09 |
| | Cigarettes only | 8 | 0.13 (0.09-0.17) | | 4.69 |
| Unexposed | Never cigarettes | 4 | 0.19 (0.13-0.25) | NS | 9.05 |
| | Never any product | 23 | 0.17 (0.15-0.20) | | 7.66 |
| Grouped midpoint age (yr) | < 50 | 7 | 0.18 (0.13-0.23) | NS | 7.73 |
| | 50-59 | 9 | 0.21 (0.17-0.25) | | 10.98 |
| | 60+ | 11 | 0.17 (0.14-0.19) | | 6.88 |
| Cases in smokers | < 100 | 12 | 0.14 (0.11-0.17) | < 0.001 | 5.09 |
| | 100 to < 200 | 7 | 0.20 (0.16-0.24) | | 9.88 |
| | 200 to < 500 | 4 | 0.17 (0.23-0.20) | | 7.02 |
| | 500 to < 1000 | 3 | 0.23 (0.20-0.26) | | 14.57 |
| | 1000+ | 1 | 0.15 (0.11-0.19) | | 5.71 |

[1]Probability values for factor considered, presented as < 0.001, < 0.01, < 0.05, < 0.1 or not significant (NS) ($P \geqslant 0.1$); [2]Of principal publication for the study; [3]Any product = Smokes cigarettes and/or pipes and/or cigars; Cigarettes +/- = Smokes cigarettes with or without other products (pipes, cigars).

membering smoking history also form part of the problem. Also the dose of smoke constituents received may not be directly proportional to the amount smoked[15].

### Misclassification of duration and age of starting

Subjects may not remember the exact age of starting, and indeed there may be differences in definition between studies - age of first trying a cigarette, or age of starting to smoke regularly? Also duration may not represent a continuous period. Risk may be affected by intermediate quit periods, which may be asked about differently in different studies.

### Estimating midpoints of ranges

The statistical methods used require estimates of midpoints of ranges used. We have not attempted sensitivity analyses based on alternative procedures for defining midpoints.

### Use of pseudo-numbers

Our methodology requires knowledge, for each block, of the numbers of cases and controls (or at risk) in each smoking group. As such data are not always provided, and indeed for covariate-adjusted data are only hypothetical, we used the method of Hamling *et al*[4] to estimate pseudo-numbers corresponding exactly to the reported RRs and CIs. These pseudo-numbers have been shown[16] to allow accurate estimation of RRs and CIs relative to a different base group from that used originally, and should be adequate for model fitting. This issue seems less important than others considered so far.

### Adjustment for other smoking variables

Our analyses compare risk relative to never smokers, all the RRs in any block being adjusted for the same variables. As RRs relative to never smokers cannot be adjusted for other smoking variables, we necessarily restricted attention to estimates adjusted for age and non-smoking characteristics. This is possibly unfortunate as, for example, later starters may smoke less than earlier starters. In theory one could study the extent of such bias based on studies presenting risk (compared to never smokers) jointly by more than one dose measure. However, few studies present such data and we did not investigate this.

### Use of simple models based on published results

We restricted attention to models of a relatively simple functional form, partly as it is much easier to explain results and conduct tests of heterogeneity where differences between blocks can be expressed in terms of one parameter ($\beta_1$). Also, the numerous data uncertainties may not justify a more complex approach. Such an approach is better pursued using individual person data from large studies. This would allow fitting of models simultaneously accounting for amount smoked and duration, and allow a more precise risk estimation. In the context of a systematic review and meta-analysis, involving many studies conducted years ago with the data unlikely to be accessible, we made no attempt to obtain individual data sets.

### Model fit

Goodness-of-fit has been studied in various ways. First, we used the "pool-first" approach[9,10] to compare the deviance of models with a common $\beta_1$ per block but a different functional form of the dose-relationship. The exponential (log RR = $\beta_1$exp d) and the log model (log RR = $\beta_1$log d) clearly fitted substantially worse than other models, and were not pursued further. Also, the power model (log RR = $\beta_1 d^Y$) and the log-with-baseline model [log RR = $\beta_1$log (1 + Wd)] generally fitted better than the linear model (log RR = $\beta_1$d), though for age of starting the best-fitting log-with-baseline model had such a low estimate of W that it became equivalent to the linear model. While the deviance of the linear model was reduced by adding quadratic and cubic terms this advantage was small. We concentrated most on the power and/or log-with-baseline models, given their greater simplicity, and the fact that the cubic model fitted worse than these alternatives for amount smoked and not materially better for duration or age of start.

We then restricted attention to the linear, power and, except for age of start, the log-with-baseline model, fitting separate $\beta_1$ values to each block. We investigated goodness-of-fit by studying plots of observed and predicted RRs (not shown), and by comparing observed and predicted numbers, both within block (Fit Amount Smoked[11], Fit Duration, and Fit Age Start[11]) and summed over block (Tables 4, 9 and 14). This allowed two general conclusions. First, the best models (log-with-baseline for amount smoked, power for duration and age of start) fitted the shape of the dose relationship well. Given the large number of cases analyzed (54245 for amount smoked, 10711 for duration and 7575 for age of start) it is unsurprising that formal misfit existed for amount smoked and duration, but this seems relatively unimportant. Second, there were significant misfits for some blocks. The results section comments on the worst cases. Sometimes these are due to unusual response patterns, difficult to fit by any plausible model, sometimes to differing response patterns in different blocks. Thus, for amount smoked, there are some blocks where the slope flattens off at high consumption, but others where the reverse is true. The explanation for this is unclear, but attempting to account for it by more complex models seems unattractive, as compared to the models selected, which involve a common shape and variation only in slope ($\beta_1$).

### Sources of heterogeneity

We carried out weighted regression analyses to investigate sources of heterogeneity. While some factors (*e.g.*, age and sex) could be better evaluated using pooled analyses based on individual person data, and problems arise from correlations between variables studied, these analyses should detect major sources.

For amount smoked, these analyses only identified

continent as a significant factor, other associations seen in the simple analyses becoming non-significant once continent was accounted for. The smaller $\beta_1$ for Asian studies is consistent with our earlier analyses[16], and may relate to higher denial rates of smoking in Asia.

For duration and age of starting, the regression analyses showed a tendency for $\beta_1$ to be greater in studies involving more lung cancer cases and studies of younger people. Higher values in males than females and lower values in Asian studies were not independently significant. There was also some evidence for duration of higher $\beta_1$ values for smoking cigarettes, than smoking any product.

### Comparison with some previous work

Attempts have been made before to model the relationship of lung cancer to amount smoked and duration. For example, Doll *et al*[17], in a much cited paper, based on data for British doctors who started smoking at ages 16-25 and smoked 40 or less per day, modelled the annual lung cancer incidence at age 40-79 by the expression

$0.273 \times 10^{-12} \times (\text{cigarettes/d} + 6)^2 \times (\text{age} - 22.5)^{4.5}$.

They noted "significant ($P < 0.01$) upward curvature of the dose-response relationship in the range 0-40 cigarettes/d, which is what might be expected if more than one of the 'stages' (in the multistage genesis of bronchial carcinoma) was strongly affected by smoking." They also noted a drop off in response above 40 cigarettes/d, though based on few cases, and discussed various explanations for it. Our analyses show little evidence of upward curvature with amount smoked. However, this does not rule out smoking affecting more than one stage of a multistage process; indeed there is strong evidence this is true[18].

Taking (age - 22.5 years) as an approximate indicator of duration, the model of Doll *et al*[17] suggests risk rises steeply with increasing duration, according to a fourth or fifth power relationship. At first sight, this appears to conflict with our findings, where the power relationship we fitted was only somewhat above linear (Figure 1C). However, whereas Doll and Peto's analysis compares risk by age for people of a similar age of start, our modelling compares risk by age of start for people of a given age. Here, the relationship of risk to duration will be much less steep. This can be illustrated by applying formulae for a form of the multistage model where risk affects the first and penultimate stages, the effect on the penultimate stage being twice as strong as for the first stage, a form known to fit smoking and lung cancer relationships quite well[18,19]. The RR for a 70-year-old starting at age 15 is estimated as 1.66 times higher than for a 70-year-old starting at age 30. This ratio somewhat exceeds the ratio of durations (55/40 = 1.38), but much less than predicted by a fourth or fifth power relationship ($1.38^{4.5} = 4.26$).

### Summing up

Based on 71 studies described in 87 publications[20-106] we demonstrated that for all three measures of dose studied (amount smoked, duration and age of start), the shape of their relationship with lung cancer can be described quite accurately using simple models. Though, for all dose measures, there is evidence of misfit for some data blocks, these seem mainly due to unusual response patterns difficult to fit with plausible models, or to different blocks showing differing shapes of the dose-relationship. The main limitations of the models relate to the data they were fitted to. Misclassification of smoking status and of dose may produce bias, as may failure to update smoking habits during follow-up in prospective studies, and failure to adjust for other indices of dose. Nevertheless, the models presented characterize the observed relationships of lung cancer to amount smoked, duration, and age of start more fully than previously attempted.

## ACKNOWLEDGMENTS

We thank Philip Morris Products S.A. for supporting this research. The opinions and conclusions of the authors are their own, and do not necessarily reflect the position of Philip Morris Products S.A. We also thank Pauline Wassell, Diana Morris and Yvonne Cooper for assistance in typing various drafts of the paper and obtaining relevant literature.

## COMMENTS

### Background

No previous meta-analysis has used parametric models in order to quantify more precisely the relationship between smoking and lung cancer. Using a database of all epidemiological studies of 100 or more lung cancer cases published before 2000, models are fitted relating lung cancer risk to amount smoked, duration of smoking and age of starting to smoke.

### Research frontiers

Based on all the studies providing relevant data, the models fitted show that the risk, relative to never smokers, rises from 3.86 to 22.31 between 10 and 50 cigarettes/d, from 2.21 to 13.54 between 10 and 50 years smoked, and from 3.66 to 8.94 between age of starting 30 and 12.5 years. There is little heterogeneity between studies for duration of smoking or age started, but there is clear heterogeneity for amount smoked, with RRs for 50 cigarettes/d being 7.23 for studies in Asia, as compared to 26.36 for North American and 22.16 for European studies.

### Innovations and breakthroughs

The new feature of this paper is the comprehensive assessment of the shape of the dose-responses studied, with a number of alternative functional forms studied, and the best-fitting one selected. The fitted models, which describe the relationships well, are each quite simple in form, allowing ready meta-analysis of individual study estimates.

### Applications

The fitted models allow more precise quantification of the hazards of smoking than previously reported, and will assist smoking and health researchers.

### Terminology

Linear model: The logarithm of the RR is linearly related to dose. In the power model it is related to dose raised to a power. In the log-with-baseline model, it is related to the logarithm of dose with an offset for background risk. Pseudo-numbers are estimates of numbers of cases and controls, by dose level, derived from published RRs, which allow fitting of the models.

### Peer review

The authors meta-analyzed smoking/lung cancer relationships using parametric modelling according to the IESLC database. They found that the models describe the dose-relationship well and concluded that they can be used to more precisely estimate the lung cancer risk from smoking. The limitation has been fully discussed in the discussion part. This study provides some interesting results for further research into smoking and lung cancer.

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**P- Reviewers** Iftikhar IH, Shen XC, Zhang J **S- Editor** Gou SX
**L- Editor** A **E- Editor** Zheng XM

World Journal of Meta-Analysis

Online Submissions: http://www.wjgnet.com/esps/
wjma@wjgnet.com
doi:10.13105/wjma.v1.i2.78

*World J Meta-Anal* 2013 August 26; 1(2): 78-82
ISSN 2308-3840 (online)


META-ANALYSIS

# Ophthalmic adverse drug reactions: A nationwide detection using hospital databases

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Received: February 4, 2013 Revised: June 10, 2013
Accepted: July 18, 2013
Published online: August 26, 2013

## Abstract

**AIM:** To detect ophthalmic adverse drug reactions (ADRs), that occurred in Portugal from 2000 to 2009, through the utilization of administrative hospital databases. We also intended to compare the results of this methodology with spontaneous reporting.

**METHODS:** We conducted a retrospective nationwide study using hospital administrative databases, which included all inpatients and outpatients in all public hospitals in Portugal, from 2000 to 2009. We used International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM) coding data that allowed the detection of ADRs. We used WHO's definition for ADR. We searched all of ICD-9-CM terms in Ophthalmology for codes that included "drug-induced", "iatrogenic", "toxic" and all other that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responders", and also "E" codes (codes from E930 to E949.9, that exclude intoxications and errors).

**RESULTS:** From 11944725 hospitalizations or ambulatory episodes within that period of time, we identified 1524 probable ophthalmic ADRs (corresponding to a frequency of 1.28 per 10000 episodes) and an additional 100 possible ophthalmic ADRs. We used only 4 person-hours in the application of this methodology. A total of 113 spontaneous reports arose from ophthalmic ADRs from 2000 to 2009 in Portugal (frequency of 0.095 per 10000 episodes).To our knowledge, this was the first estimate of the frequency of ophthalmic ADRs through the use of databases, and the first nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs.

**CONCLUSION:** This database methodology adapted for Ophthalmology may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification. Its performance was clearly superior to spontaneous reporting.



**Key words:** Adverse drug reactions; Ophthalmology; Ocular; Databases; Pharmacovigilance

**Core tip:** We used International Classification of Diseases - 9th Revision - Clinical Modification coding data for the detection of adverse drug reactions (ADRs). From 11944725 episodes, we identified 1524 probable ophthalmic ADRs. 113 spontaneous reports arose from that population. This was the first nationwide study of ophthalmic ADRs and may represent a new Pharmacovigilance approach, with a higher detection than spontaneous reporting.

Miguel A, Henriques F, Marques B, Marques J, Freitas A, Lopes F, Azevedo L, Pereira AC. Ophthalmic adverse drug reactions: A nationwide detection using hospital databases. *World J Meta-Anal* 2013; 1(2): 78-82 Available from: URL: http://www.

wjgnet.com/2308-3840/full/v1/i2/78.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i2.78

## INTRODUCTION

Adverse drug reactions (ADRs) are responsible for significant morbidity, mortality and costs in Health Care systems[1]. They may occur in 16.9% of patients during hospitalization (95%CI: 13.5-20.2)[2] and provoke 5.3% of hospital admissions (interquartile range 2.7%-9.0%)[3]. ADRs are a frequent cause of death in developed countries[4]. However, in Ophthalmology the evidence is scarce and lacks systematization[5]. A review about challenges in ADRs in Ophthalmology[5] concluded that there are several areas that can be improved, namely by applying always the definition of ADR of the World Health Organization (WHO)[6], by performing a causality assessment in each ADR (which determines the probability of representing a true ADR; the most utilized causality assessments of ADRs are from WHO[7] and from Naranjo *et al*[8]).

The development and validation of new methodologies for an improved detection of ADRs would be another area of improvement[5,9]. There are Pharmacovigilance methodologies[9] used for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues: Spontaneous reporting is the most used (it needs low resources) and is the only Pharmacovigilance method continuously used in the majority of countries, being the main support of WHO International Drug Program. However, it has several limitations, namely, the smallest detection rate of several Pharmacovigilance methods[10], under-reporting[11], heterogeneous report quality[12] and increased risk of bias[12]. Intensive and prospective monitoring are methodologies with good detection rates but too resource-consuming for continuous application[13].

Administrative hospital databases have large clinical information and thus may represent an interesting Pharmacovigilance approach with readily available and cheap information[10]. Some authors have utilized databases[10,14] for the detection of ADRs, taking advantage of the large quantity of clinical information readily available, containing coding data that can be used as an alert for the detection of an ADR, with low relatively low resources required.

Our purpose was to identify and characterize ophthalmic ADRs in a Nationwide study in Portugal, using hospital databases with clinical information.

## MATERIALS AND METHODS

### Study design

A retrospective study was performed for ADR identification using hospital administrative databases with information from all public hospitals in Portugal, from 2000 to 2009, obtained from our National Health Department (data from the second semester of 2009 was not available). These databases contain anonymized data for patient identification, episode and process number, and also information on age, sex, admission date, discharge date, ward(s), hospital attended (tertiary, university), area of Healthcare, district, outcome (death, discharge, transfer), payment data and International Classification of Diseases - 9th Revision - Clinical Modification (ICD-9-CM)[15] codes for: diagnoses (principal diagnosis, other diagnosis up to 19), procedures (up to 20) and external causes (up to 20). Patient population included all patients hospitalized or admitted for ambulatory care, in all public hospitals in Portugal, from 2000 to 2009 (inpatients and outpatients). All investigations were performed according to the guidelines of the Declaration of Helsinki and Institutional Review Board approval from was obtained.

### Definition of ADR

There is some misuse of terms in this matter; therefore we present definitions.

An ADR[6] is: "any noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy". Therefore, to increase specificity, we wanted to assess only ADRs. Adverse drug event is not a synonym of ADR. There are other definitions of ADR, namely from Karch *et al*[16] and from Edwards *et al*[17], but we used the definition of WHO. An adverse event[18] is: "an injury related to medical management (all aspects of care, including diagnosis and treatment, failure to diagnose or treat, and the systems and equipment used to deliver care), in contrast to complications of disease". An adverse drug event[19] is: "An injury related to the use of a drug, although the causality of this relationship may not be proven". These include medication errors (namely the prescription of a wrong dose) and ADRs. We aimed to assess strictly ADRs.

### Detection of ADRs

Hospital administrative databases include information of diagnosis. Codes searched for ADR identification were adapted to the specificities of Ophthalmology and resulted from a thorough search of: all terms of ICD-9-CM in Ophthalmology that included "drug-induced", "iatrogenic", "toxic" and all codes that could signal an ADR, such as "362.55 - toxic maculopathy" or "365.03 - steroid responsers", as detailed in the Results Section.

We also performed a search of general ADRs through the use of 'E' codes (ICD-9-CM codes from E930 to E949.9, designed to represent ADRs and already excluding wrong doses, errors and intoxications) to assess if these general ADRs could detect ophthalmic ADRs.

In this study, we performed a query of Ophthalmology in a nationwide study using administrative databases, including inpatients and ambulatory patients. Our main outcome was ADR detection. Secondary outcomes included: type of ADR, age, sex, admission diagnosis, other diagnoses, hospital length-of-stay and year of discharge. We performed WHO's causality assessments of ADRs,

with two independent reviewers. Differences were resolved by consensus. A third review was consulted to help resolved differences. We also registered how many person-hours were spent in the application of this methodology, to estimate cost (resources spent). The number of person-hours refers to the number of hours and number of people used in the application of this methodology; commonly used in the comparison of different Pharmacovigilance methodologies[19]. The number of spontaneous reporting of ADRs in hospitalized patients from 2000 to 2009 was obtained from Portuguese National Authority of Medicines (INFARMED), for comparison[20].

### Statistical analysis

Statistical analyses were done using the $\chi^2$ test for categorical variables (or exact Fisher's test whenever possible), Student's *t*-test for normally distributed continuous variables and Mann-Whitney or Kruskal-Wallis for variables without normal distribution, using SPSS v20. The a priori level of significance was $P < 0.05$.

## RESULTS

### Study population

There were 11944725 patients hospitalized or with ambulatory episodes in public hospitals of Portugal, from 2000 to the first semester of 2009. The baseline characteristics of the study population ($n$ = 11944725) are shown in Table 1. The mean age of hospitalized patients was 48 ± 27 years and in 55.2% of episodes the patient was female. We spent only 4 person-hours in the application of this methodology.

From 2000, there was a slight increase in the number of hospitalizations in Portugal. Specific ophthalmic ADRs ($n$ = 1524) were detected through the search of codes that could represent particular ophthalmic ADRs, as shown in Table 2. This corresponds to a frequency of 1.28 ophthalmic ADR per 10000 episodes. Additionally, 100 episodes that could possibly correspond to an ophthalmic ADR were also detected (Table 2). Therefore, a total of 1624 possible ophthalmic ADRs were detected. These possible ADRs included: conjunctival concretions, pigmentations and deposits (which can be caused by drugs such as topical adrenaline[21], but also by other factors, therefore may correspond to an ADR in some cases) and acquired color vision deficiencies (which may be caused by drugs such as sildenafil[22], but have other non related causes).

The search of general ADRs through the use of "E" codes allowed us to identify 116720 ADRs, but only 62 of them corresponded to the ophthalmic ADRs that were identified.

The total number of spontaneous notifications of ADRs in Portugal from 2000 to 2009 was 13562, from which 113 were spontaneous reports specific of ophthalmic ADRs. There were 553 additional spontaneous reports of systemic ADRs that included some ophthalmic manifestations.

**Table 1 Socio-demographic characteristics of study population**

| Characteristic | Value |
|---|---|
| Number of episodes (inpatient, ambulatory) | 11944725 |
| Mean age (yr, mean ± SD) | 48 ± 27 |
| Female gender n (%) | 6598266 (55.2) |
| District with higher number of hospitalizations | 1st: Lisbon 21.2%<br>2nd: Oporto 17.2%<br>3rd: Setubal 7.66% |
| Mean hospital length-of-stay for inpatients (d, mean ± SD) | 7.1 ± 3.21 |
| Number of probable ophthalmic ADRs | 1524 |

ADRs: Adverse drug reactions.

**Table 2 Clinical codes searched and respective results in the portuguese database**

| ICD-9-CM code | Diagnosis | No. of episodes |
|---|---|---|
| Specific ophthalmic ADR codes | | |
| 362.55 | Toxic maculopathy | 1388 |
| 365.03 | Steroid responders | 4 |
| 365.31, 365.32 | Corticosteroid-induced glaucoma | 0 |
| 364.55 | Miotic pupillary cyst (provoked by pilocarpine) | 2 |
| 364.81 | Floppy iris syndrome | 2 |
| 366.45 | Toxic cataract | 83 |
| 367.89 | Other drug-induced disorders of refraction and accommodation, Toxic disorders of refraction and accommodation | 25 |
| 377.34 | Toxic optic neuropathy, Toxic amblyopia | 20 |
| Possible signs of ophthalmic ADRs | | |
| 366.46 | Cataract associated with radiation and other physical influences | 10 |
| 372.54 | Conjunctival concretions | 67 |
| 372.55 | Conjunctival pigmentations, including conjunctival argyrosis | |
| 372.56 | Conjunctival deposits | |
| 368.55 | Acquired color vision deficiencies | 23 |
| 368.59 | Other color vision deficiencies | |
| | Sub-Total specific | 1524 |
| | Total | 1624 |

ICD-9-CM: Classification of Diseases - 9th Revision - Clinical Modification; ADRs: Adverse drug reactions.

## DISCUSSION

To our knowledge, this is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal. We identified 1524 probable ADRs and 100 possible ADRs. This may represent a new approach for the detection of ophthalmic ADRs, since these codes exist in the ICD-9-CM classification.

The strengths of our study include: our comprehensive database, which contains data from all hospitalizations and ambulatory episodes in every public hospital in Portugal within almost a decade, the fact that this is a new methodology to aid ADR detection (until now only case reports and spontaneous reports were available for

ADR detection), and the fact that these codes are widely available and universal, making possible to easily build estimates of ophthalmic ADRs in other countries and other years. In fact, it would be very interesting to see if ophthalmic ADRs in Portugal have the same distribution, frequency and characteristics in comparison with other countries, therefore further studies are necessary.

Limitations of our work are inherent to the use of administrative databases, which may contain incomplete or wrong data and coding bias[23] (in which coders select a different code to increase reimbursement to their hospital). The small number of ADRs found may be considered a limitation, but on the other hand this is a methodology resource-sparing (only 4 person-hours spent in its application), having potential for widespread application in other countries. Also, this method identified 1524 probable ADRs, a much higher number than the number of ophthalmic ADRs found by spontaneous reporting: 113.

We suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs. In fact, the complementary use of several methodologies is defended by several authors[24], in order to enhance ADR detection and increase patient safety. Finally, we believe that after this study, these codes should be applied prospectively in a future study in a nation-wide basis, enabling an expert to confirm each ADR and causing drug, to further complete and validate the data suggested here, and to integrate this method as a Pharmacovigilance methodology.

In conclusion, Ophthalmology represents simultaneously a challenge and an opportunity to identify ADRs. This is the first nationwide estimate of ophthalmic ADRs. Administrative databases are a useful methodology for the detection of ocular ADRs, but require adapted diagnoses codes. They may underestimate the real number of ADRs, but nevertheless they have the potential to complement spontaneous reporting as a methodology for ophthalmic ADR detection, with a higher detection rate.

## ACKNOWLEDGMENTS

The authors would like to thank ACSS for providing access to the data, and express gratitude to the statistical support given by the research project HR-QoD - Quality of data (outliers, inconsistencies and errors) in hospital inpatient databases: methods and implications for data modeling, cleansing and analysis (project PTDC/SAU-ESA/75660/2006). The authors would also like to thank the INFARMED, Portuguese National Authority of Medicines and Health Products, for the data kindly provided about spontaneous reporting in Portugal.

## COMMENTS

### Background

Adverse drug reactions (ADRs) are a frequent cause of death in developed countries. However, in Ophthalmology the evidence is scarce and lacks systematization.

### Research frontiers

There are Pharmacovigilance methodologies used for the detection of ADRs and that can be adapted for detecting ADRs in Ophthalmology, but they may have methodological issues.

### Innovations and breakthroughs

This is the first estimate of the frequency of ophthalmic ADRs through the use of administrative databases, and the first to apply a nationwide estimate of ophthalmic ADRs, in Portugal.

### Applications

The authors suggest complementing spontaneous reporting with this database methodology to increase detection of ophthalmic ADRs.

### Peer review

This is a well written article reporting the adverse effects of ophthalmic drugs. The methods are well described, and the results are easy to understand.

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**P- Reviewers** Onakpoya I, Saokaew S **S- Editor** Zhai HH
**L- Editor** A **E- Editor** Zheng XM

World Journal of Meta-Analysis

Online Submissions: http://www.wjgnet.com/esps/
wjma@wjgnet.com
doi:10.13105/wjma.v1.i2.83

*World J Meta-Anal* 2013 August 26; 1(2): 83-89
ISSN 2308-3840 (online)




# Prevalence of hypertension in India: A meta-analysis

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Received: April 24, 2013 Revised: July 18, 2013
Accepted: August 4, 2013
Published online: August 26, 2013

## Abstract

**AIM:** To determine the prevalence of hypertension in the urban and rural population of India.

**METHODS:** Relevant studies were identified through computer based and manual searches using MEDLINE/PubMed, Google scholar, EMBASE, Cochrane Library and reference lists of prevalence studies from January 2000 to June 2012. A total of 12 studies were included in the meta-analysis of hypertension in urban India and 10 studies in the analysis of hypertension in rural India after applying the inclusion and exclusion criteria. Estimates of prevalence were calculated using the random effect model for meta-analysis.

**RESULTS:** The electronic search using appropriate keywords identified 177 titles for prevalence of hypertension in urban India, of which 165 were excluded, and 133 titles for prevalence in rural India, of which 123 were excluded after applying the inclusion criteria. Twelve studies including 125333 subjects were analyzed to assess the prevalence of hypertension in the urban Indian population, whereas ten studies including 24800 subjects were analyzed to determine the prevalence of hypertension in the rural Indian population. The prevalence of hypertension in the urban population was estimated to be 40.8% (95%CI: 40.5%-41.0%) and that of hypertension in the rural population was 17.9% (95%CI: 17.5%-18.3%). It is evident that the prevalence of hypertension is significantly higher in the urban population of India compared to the rural.

**CONCLUSION:** Current evidence suggests that policies and interventions should be prioritized for reduction of hypertension in the adult Indian population, especially the urban population.



**Key words:** Prevalence; Hypertension; Meta-analysis; India; Urban; Rural

**Core tip:** A meta-analysis of prevalence studies on hypertension in India from January 2000 to June 2012 reveals a high prevalence of hypertension in the urban (40.8%) as well as rural population (17.9%). The prevalence of hypertension is markedly higher in the urban population compared to the rural population, but the prevalence in the rural population is also a matter of concern with almost every fifth individual at risk. This is indicative of the epidemiological transition, which must raise an alarm for policy makers and health care professionals. Primordial and primary prevention of hypertension can bring about a substantial reduction in cardiovascular morbidity and mortality which occurs as a consequence of hypertension.

Midha T, Nath B, Kumari R, Rao YK, Pandey U. Prevalence of hypertension in India: A meta-analysis. *World J Meta-Anal* 2013; 1(2): 83-89 Available from: URL: http://www.wjgnet.

com/2308-3840/full/v1/i2/83.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i2.83

## INTRODUCTION

Globally, the overall prevalence of hypertension or raised blood pressure in adults aged 25 and above was around 40% in 2008[1]. Worldwide, hypertension is estimated to cause 7.5 million deaths, about 12.8% of the total deaths. Hypertension accounts for 57 million disability adjusted life years (DALYS) or 3.7% of total DALYS[1]. The World Health Organization (WHO) has estimated that globally about 62% of cerebrovascular diseases and 49% of ischemic heart diseases are attributable to suboptimal blood pressure (systolic > 115 mmHg), with little variation by sex[2]. One in three adults worldwide has high blood pressure. Hypertension increases the risk of heart attack, stroke, kidney failure and many other associated co morbidities. Treating raised blood pressure and maintaining it below 140/90 mmHg is associated with a reduction in cardiovascular complications[1].

The theme for World Health Day (WHD) 2013 is "high blood pressure"[3]. The goal of WHD 2013 is to reduce heart attacks and strokes. Keeping in line with the WHO-Government of India Country Cooperation Strategy, the WHD 2013 events in India are aimed at raising the awareness amongst national policymakers, program managers and other stakeholders on the need to strengthen the Indian health system to make it competent enough to respond to hypertension and related co morbidities[3].

Hypertension is a controllable disease and it has been reported that targeted reductions in people with hypertension are expected to produce large reductions in the burden of cardiovascular disease[4]. According to the seventh report of the Joint National Committee (JNC-7) on prevention, detection, evaluation and treatment of high blood pressure, adoption of healthy lifestyles by all individuals is critical for the prevention of high blood pressure[5]. Accurate estimates of hypertension are therefore necessary to plan effective control measures.

A meta-analysis showed an increase in the prevalence of hypertension in India over the years from 1%-3% in 1950 to 10%-30.9% in 2002[6]. Another cause for concern is the epidemiological transition, as it is likely that the prevalence of risk factors, and consequently the prevalence of hypertension and cardiovascular diseases, would rise with the socioeconomic development of rural areas in India.

India accounts for 17% of the world's population, the second largest in the world, and hence it contributes largely to the statistics of any disease in the world[7]. Given the fact that hypertension is on the rise in developing countries like India, this meta-analysis was designed to consolidate the available data to find out the current prevalence of hypertension in urban and rural India.

## MATERIALS AND METHODS

### Search strategy

We searched MEDLINE/PubMed, Google scholar, EMBASE, Cochrane Library and reference lists of prevalence studies from January 2000 to June 2012. Internet searches used permutations of medical subject headings for prevalence studies on hypertension in India. The following keywords were looked for individually or in association: hypertension, India, prevalence, blood pressure, systolic, diastolic, mmHg. The limits included were: English for the language category and humans for the study category (Figure 1).

### Selection criteria

The studies that met all of the following criteria were included in the present meta-analysis: (1) they were prevalence studies; (2) the study design was cross-sectional; (3) the age group included in the study was 20 years and above; (4) the study was conducted in the Indian population; (5) the cut-off for classification of hypertension was systolic blood pressure $\geqslant$ 140 mmHg and/or diastolic blood pressure $\geqslant$ 90 mmHg; and (6) the study contained original data. All the studies had a cross-sectional design and blood pressure measurement on a single visit was considered. Exclusion criteria: reviews, letters to editors, case series and case-control studies were not included because of insufficient data for analysis.

### Statistical analysis

Data was analyzed using the statistical software Comprehensive Meta-analysis V2. The random effect model was used to calculate the estimate of the prevalence of hypertension rather than the fixed effect model. The random effect model takes into account any heterogeneity inherent in the meta-analysis.

## RESULTS

### Literature review

The electronic search in Pubmed, using the keywords "prevalence of hypertension in urban India", identified 177 titles, of which 165 were excluded based on review of titles, abstracts and text after applying the inclusion criteria. To avoid bias due to selection criteria and blood pressure criteria used in various studies, age, blood pressure cut-off and study design criteria were taken into consideration. The remaining 12 studies were included in the analysis. Similarly, following electronic search in Pubmed, using the keywords "prevalence of hypertension in rural India", we identified 133 titles, of which 123 were excluded based on review of titles, abstracts and text after applying the inclusion criteria. The remaining 10 were included in the analysis.

### Study characteristics

In total, 12 studies were included in the meta-analysis of hypertension in urban India and 10 studies in the analysis of hypertension in rural India.

**Table 1 Review of studies on the prevalence of hypertension**

| First author | Place | Age group (yr) | Sample size | Prevalence |
|---|---|---|---|---|
| In the urban Indian population | | | | |
| Anand[10] | Maharashtra | 30-60 | 1662 | 34.0 |
| Gupta *et al*[11] | Rajasthan | > 20 | 1123 | 33.4 |
| Shanthirani *et al*[12] | Tamil Nadu | > 20 | 1262 | 21.1 |
| Gupta *et al*[18] | Maharashtra | > 35 | 88653 | 47.9 |
| Prabhakaran *et al*[16] | Delhi | 20-59 | 2935 | 30.0 |
| Reddy *et al*[13] | Multi-centric | 20-69 | 19973 | 27.7 |
| Mohan *et al*[14] | Tamil Nadu | > 20 | 2350 | 20.0 |
| Kaur *et al*[15] | Tamil Nadu | 18-69 | 2262 | 27.2 |
| Yadav *et al*[33] | Uttar Pradesh | > 30 | 1746 | 32.2 |
| Midha *et al*[17] | Uttar Pradesh | > 20 | 400 | 32.8 |
| Gupta[27] | Multi-centric | 35-70 | 926 | 48.2 |
| Chakraborty *et al*[9] | West Bengal | 18-60 | 433 | 17.6 |
| In the rural Indian population | | | | |
| Kusuma *et al*[31] | Andhra Pradesh | > 20 | 1316 | 21.0 |
| Hazarika *et al*[30] | Assam | > 30 | 3180 | 33.3 |
| Midha *et al*[17] | Uttar Pradesh | > 20 | 400 | 14.5 |
| Todkar *et al*[19] | Maharashtra | > 20 | 1297 | 7.2 |
| Bhardwaj *et al*[24] | Himachal Pradesh | > 18 | 1092 | 35.9 |
| Kinra *et al*[32] | Multi-centric | 20-69 | 1983 | 20.0 |
| Rajasekar *et al*[20] | Tamil Nadu | > 30 | 1905 | 19.1 |
| Kadu *et al*[21] | Maharashtra | > 18 | 2196 | 12.8 |
| Bansal *et al*[22] | Uttarakhand | > 15 | 968 | 32.3 |
| Kaur *et al*[23] | Tamil Nadu | 25-64 | 10463 | 21.4 |

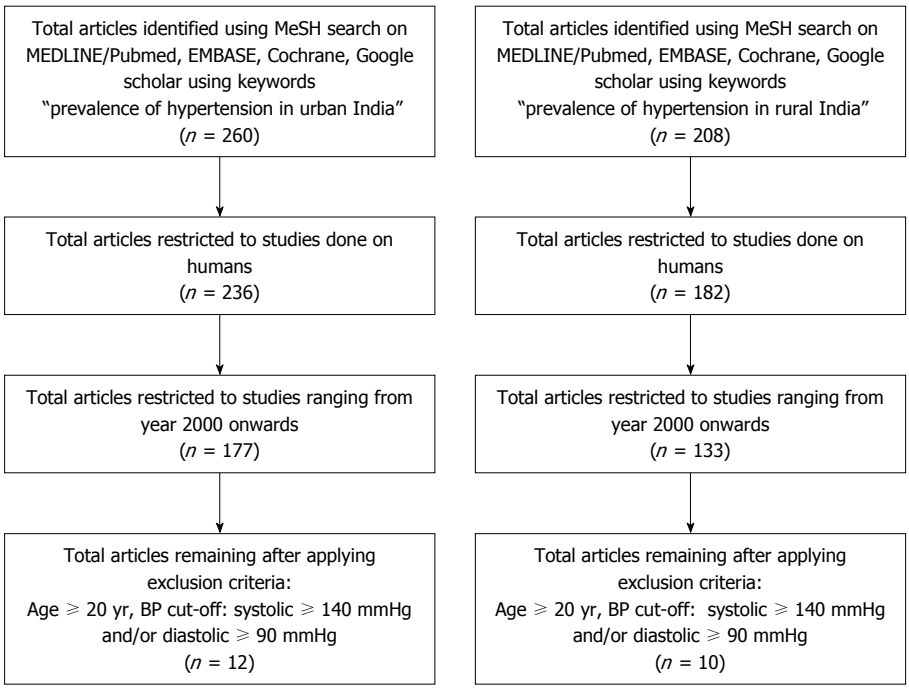


**Figure 1 Flow diagram of selection process.** Course of systematic literature review on prevalence of hypertension in urban and rural India. BP: Blood pressure.

### *Meta-analysis*

After analysis of 125333 subjects from twelve studies, the prevalence of hypertension in the urban Indian population was found to be 40.8% (95%CI: 40.5%-41.0%) (Table 1). Ten studies including 24800 subjects were analysed and the prevalence of hypertension in the rural population was estimated to be 17.9% (95%CI: 17.5%-18.3%) (Table 1). Figure 2 shows the meta-analysis of prevalence of hypertension in the urban and rural Indian population respectively. The overall prevalence rate is represented by the random effect size which was estimated to be 40.8% in urban and 17.9% in the rural population.

## DISCUSSION

In the present meta-analysis, the prevalence of hypertension was estimated to be 40.8% in urban and 17.9% in

**A**

Meta Analysis

| Study name | Statistics for each study | | | | | | |
|---|---|---|---|---|---|---|---|
| | Point estimate | SE | Variance | Lower limit | Upper limit | *Z*-value | *P*-value |
| Anand[10] | 34.00 | 1.160 | 1.34 | 31.72 | 36.27 | 29.310 | 0.000 |
| Gupta *et al*[11] | 33.40 | 1.410 | 1.98 | 30.63 | 36.16 | 23.688 | 0.000 |
| Shanthirani *et al*[12] | 21.10 | 1.150 | 1.32 | 18.84 | 23.35 | 18.348 | 0.000 |
| Gupta *et al*[18] | 47.90 | 0.170 | 0.02 | 47.56 | 48.23 | 281.765 | 0.000 |
| Prabhakaran *et al*[16] | 30.00 | 0.850 | 0.72 | 28.33 | 31.66 | 35.294 | 0.000 |
| Reddy *et al*[13] | 27.20 | 0.310 | 0.09 | 26.59 | 27.80 | 87.742 | 0.000 |
| Mohan *et al*[14] | 20.00 | 0.830 | 0.68 | 18.37 | 21.62 | 24.096 | 0.000 |
| Kaur *et al*[15] | 27.20 | 0.940 | 0.88 | 25.35 | 29.04 | 28.936 | 0.000 |
| Yadav *et al*[33] | 32.20 | 1.120 | 1.25 | 30.00 | 34.39 | 28.750 | 0.000 |
| Midha *et al*[17] | 32.80 | 2.350 | 2.40 | 28.10 | 37.49 | 28.725 | 0.000 |
| Gupta[27] | 48.20 | 1.640 | 2.69 | 44.98 | 51.41 | 29.390 | 0.000 |
| Chakraborty *et al*[9] | 17.60 | 1.830 | 3.34 | 14.01 | 21.18 | 9.617 | 0.000 |
| Random effect size | 40.76 | 0.137 | 0.01 | 40.49 | 41.02 | 297.873 | 0.000 |

**B**

Meta Analysis

| Study name | Statistics for each study | | | | | | |
|---|---|---|---|---|---|---|---|
| | Point estimate | SE | Variance | Lower limit | Upper limit | *Z*-value | *P*-value |
| Kusuma *et al*[31] | 21.00 | 1.100 | 1.21 | 18.84 | 23.15 | 19.091 | 0.000 |
| Hazarika *et al*[30] | 33.30 | 0.800 | 0.64 | 31.73 | 34.86 | 41.625 | 0.000 |
| Midha *et al*[17] | 14.50 | 1.500 | 0.25 | 11.10 | 17.90 | 18.600 | 0.000 |
| Todkar *et al*[19] | 7.20 | 0.700 | 0.49 | 5.82 | 8.57 | 10.286 | 0.000 |
| Bhardwaj *et al*[24] | 35.90 | 1.500 | 2.25 | 32.96 | 38.84 | 23.933 | 0.000 |
| Kinra *et al*[32] | 20.00 | 0.900 | 0.81 | 18.23 | 21.76 | 22.222 | 0.000 |
| Rajasekar *et al*[20] | 19.10 | 0.900 | 0.81 | 17.33 | 20.86 | 21.222 | 0.000 |
| Kadu *et al*[21] | 12.75 | 0.700 | 0.49 | 11.37 | 14.12 | 18.214 | 0.000 |
| Bansal *et al*[22] | 32.30 | 1.500 | 2.25 | 29.36 | 35.24 | 21.533 | 0.000 |
| Kaur *et al*[23] | 21.40 | 0.400 | 0.16 | 20.61 | 22.18 | 53.500 | 0.000 |
| Random effect size | 17.91 | 0.223 | 0.05 | 17.47 | 18.34 | 80.259 | 0.000 |

**Figure 2 The overall prevalence rate is represented by the random effect size.** A: Meta-analysis of prevalence of hypertension in the urban Indian population; B: Meta-analysis of prevalence of hypertension in the rural Indian population.

the rural Indian population. Gupta *et al*[8] reported the highest prevalence of hypertension (48.2%) in a recent multi-centric study, conducted in the urban population of India. However, Chakraborty *et al*[9] observed a lower prevalence of hypertension (17.6%) possibly because of the lower age group (18-60 years) and lower socioeconomic strata (slum dwellers) included in the study.

Anand[10] (34.0%), Gupta *et al*[11] (33.4%) and Shanthirani *et al*[12] (21.1%) in the early 2000s, and Reddy *et al*[13] (27.7%), Mohan *et al*[14] (20.0%), Kaur *et al*[15] (27.2%), Prabhakaran *et al*[16] (30.0%) and Midha *et al*[17] (32.8%) in the mid 2000s have observed that the prevalence of hypertension ranged between 20%-40% throughout the decade. However, no significant trend has been observed in the prevalence of hypertension among the studies conducted down the years. The findings of Gupta *et al*[18] reveal a prevalence of 47.9% from Mumbai, Maharashtra, probably because of the stressful lifestyle of subjects in a metropolitan city. The result of the meta-analysis summarizes all these findings and shows the prevalence of hypertension as 40.8% in the urban population of India.

In the rural population, the lowest prevalence (7.2%) was observed by Todkar *et al*[19] in Maharashtra. Midha *et al*[17] (14.5%), Rajasekar *et al*[20] (19.1%) and Kadu *et al*[21] (12.8%) have reported a lower prevalence compared to Bansal *et al*[22] (32.3%) and Kaur *et al*[23] (21.4%). Despite the lack of an obvious trend, the prevalence of hypertension in the rural population is rising swiftly to match up to the urban rates. Bhardwaj *et al*[24] reported the highest prevalence of hypertension (35.9%) in the rural population of Himachal Pradesh. The meta-analysis revealed a prevalence rate of 17.9% among the rural population.

From the available data, it is obvious that the prevalence of hypertension is higher in the urban population of India compared to the rural. No consistent trends are visible with respect to regional variations. In rural populations, the prevalence of hypertension is higher in Himachal Pradesh, while in urban studies prevalence rate is higher in Maharashtra[18,24]. The prevalence rate of hypertension was amongst the highest in metropolitan cities like Mumbai[18]. Moreover, the prevalence of hypertension in rural populations is steadily increasing and is approaching the rates of the urban population. Several studies have reported that there are significant urban-rural differences in metabolic cardiovascular risk factors[25]. Prevalence of smoking is greater in rural men while all other risk factors, such as sedentary lifestyle, obesity, central obesity, hypercholesterolemia, diabetes and the metabolic syndrome, are more common in urban men and women[26]. Most studies on urban-rural differences in cardiovascular risk factors from Haryana, Delhi, Rajasthan and Tamil Nadu have reported greater prevalence of

multiple CVD risk factors in the urban population[27]. As a result, cardiovascular diseases are epidemic in the urban regions of low income countries such as India. However, greater prevalence of cardiovascular risk factors in urban areas in India is in contrast to high income countries where the CVD risk factors are equal in urban and rural areas[28]. Similarly, it has been observed that in the more developed states of India, such as Kerala, the rural-urban differences in cardiometabolic risk factors have largely disappeared and the risk factors are equal or slightly greater in the rural population[29]. Hazarika *et al*[30] reported that even in the rural population of Assam, body mass index and waist-hip ratio were significant risk factors of hypertension. Kusuma *et al*[31] confirmed the hypothesis that acculturation/modernization may elevate the risk of hypertension and that prevalence is generally low among traditional population groups. Kinra *et al*[32] suggested that a nutrition transition (coexistence of over-nutrition and under-nutrition) may have progressed to some parts of rural India. He observed that obesity, dyslipidemia, diabetes and hypertension were more prevalent in higher socioeconomic groups in the rural areas. This epidemiological transition is a cause for serious concern as it is likely that the prevalence of risk factors, and thereby the prevalence of hypertension and cardiovascular diseases, would rise with the socioeconomic development of rural areas.

Yadav *et al*[33] observed that there was a high prevalence of cardiovascular risk factors in the general population [central obesity (86.7%), elevated LDL cholesterol (22.8%), abnormal glucose tolerance (41.6%) and smoking (20.3% of males)]. Two or more of the cardiovascular risk factors were present in a higher proportion of hypertensives (66%, OR = 3.0, $P < 0.0001$) and pre-hypertensives, (56%, OR = 2.0, $P < 0.0001$) compared to normotensive subjects (39%). The current rate of hypertension in the urban areas and the rising trend in the rural population is a warning to institute lifestyle changes in the community in order to put a halt to the increasing rates.

### Challenge ahead

The high prevalence of hypertension in the urban and rural population in India presents a formidable challenge to the Indian health system. In countries like India, the out-of-pocket expenditures incurred for non-communicable diseases (NCDs) like hypertension are high, which hits the impoverished households the most. Medicines for these chronic diseases account for a large portion of expenditure. Therefore, population based prevention strategies have a high impact and are cost-effective as these target lifestyle change. Interventions utilizing the power of public policies for reducing salt, fat, sugar and alcohol intake through regulatory and consumer education approaches; increasing physical activity through sound urban planning and creation of activity-promoting environments; increasing fruit and vegetable intake through appropriate agricultural and pricing mechanisms; and implementing comprehensive tobacco control have the potential to prevent a large proportion of disease events in the whole population[34].

Hypertension is easily diagnosable and treatable with lifestyle modifications and effective medicines. Furthermore, hypertension control provides an entry point to deal with other NCDs as any intervention will help to concomitantly address other NCDs as well. This has been taken into cognizance in the newly launched National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS), which has hypertension and diabetes as the main focus areas[34]. National strategies will focus on prevention and health promotion as the key to reduce disease burden. Health education programs that promote exercise, weight reduction, early diagnosis and screening are some of the key interventions that will be promoted at various levels of heath facilities[35]. Under the NPCDCS, the strategy for early diagnosis of chronic NCDs will consist of opportunistic screening of persons above the age of 30 years at the point of primary contact with any health care facility[35]. The NCD clinics mandated under NPCDCS could be leveraged to facilitate guidelines based hypertension management with emphasis on generic drugs and those recommended by the Indian Public Health Standards[34].

In conclusion, the high prevalence of hypertension in the urban population and a rising prevalence in the rural population must raise an alarm for policy makers and health care professionals as this is an area where primordial and primary prevention measures can bring about a substantial reduction in cardiovascular morbidity and mortality in the future.

### Limitations

Given the limited amount of data available on the prevalence of hypertension in India, studies conducted in subjects with different bio-social characteristics have been included in the meta-analysis. Nevertheless, the pooled estimate does provide an overview of the magnitude of the problem of hypertension in the Indian population.

## COMMENTS

### Background

The overall prevalence of hypertension in adults aged 25 and over was around 40% in the world in 2008 and a meta-analysis estimated a prevalence of 10-30.9% in India in 2002. This shift in epidemiological profile presents a unique challenge to India's health system as rates of cardiovascular and metabolic disease like hypertension and diabetes, obesity and cancer rise, tuberculosis, diarrheal disease and water borne illnesses remain widespread. According to a 2012 World Health Organization report, non communicable diseases are responsible for two-thirds of the total morbidity burden and about 53% of total deaths in India. Hypertension provides an entry point to other non-communicable diseases. Therefore, a precise estimate of the prevalence of hypertension in the urban and rural population of the India is required to assess the magnitude of the problem that has to be addressed.

### Research frontiers

Very few studies are available on the prevalence of hypertension in India. A consolidated estimate of hypertension from various studies conducted in different regions of the country can aid the development of preventive strategies. The difference in prevalence between the urban and rural population has also

been studied to provide an insight to the kind of preventive and promotive services required.

### Innovations and breakthroughs

It is possible that an insight into the magnitude of the problem of hypertension can help in shaping the preventive programs and policies specific for the rural and urban population.

### Applications

Very few multi-centric studies are available in India; therefore, the main application of this meta-analysis is to consolidate the available data to determine the burden of hypertension in country.

### Terminology

A meta-analysis integrates the quantitative findings from separate but similar studies and provides a numerical estimate of the overall effect of interest. Different weights are assigned to the different studies for calculating the summary or pooled effect. The weighting is related with the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in the calculation of the pooled effect size. The meta-analysis table lists the prevalence of hypertension (expressed as a percentage), with their 95%CI found in the individual studies included in the meta-analysis. The pooled proportion (prevalence) with 95%CI is given for the random effects model. The random effects model will tend to give a more conservative estimate (*i.e.*, with wider confidence interval), but the results are more valid as they take into account any inherent heterogeneity. Under the random effects model, the true effects in the studies are assumed to vary between studies and the summary effect is the weighted average of the effects reported in the different studies.

### Peer review

This manuscript is a meta-analysis on the prevalence of hypertension in India. Its results have provided evidence for policies and interventions for hypertension. It is well written.

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**P- Reviewers** Bergese SD, Tan XR **S- Editor** Wen LL
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World Journal of Meta-Analysis

Online Submissions: http://www.wjgnet.com/esps/
wjma@wjgnet.com
doi:10.13105/wjma.v1.i2.90

*World J Meta-Anal* 2013 August 26; 1(2): 90-96
ISSN 2308-3840 (online)


META-ANALYSIS

# Subclinical hypothyroidism and the metabolic syndrome: A meta-analysis of cross-sectional studies

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Received: February 20, 2013 Revised: May 23, 2013
Accepted: June 1, 2013
Published online: August 26, 2013

## Abstract

**AIM:** To determine the relationship between subclinical hypothyroidism (SCH) and the metabolic syndrome (MS).

**METHODS:** We performed a systematic search of databases [MEDLINE (July 1950 to July 2012), EMBASE (July 1966 to July 2012)] and the references of identified studies. Completely published cross-sectional studies of a general population involving SCH and the MS were included. The pooled odds ratio and weighted mean difference (WMD) for the outcomes were calculated using random-effects models.

**RESULTS:** Six cross-sectional studies with 19546 participants were included. In total, 398 of 1324 participants (30.06%) in the SCH group had the MS compared with 4975 of 18222 participants (27.30%) in the euthyroid group [OR = 1.20; 95%CI: 1.05-1.36; $P$ = 0.004; $\chi^2$ = 2.53 ($P$ = 0.773); $I^2$ = 0%]. Further analysis of the components of the MS showed that SCH was associated with increased body mass index (WMD, 0.32 kg/m$^2$; 95%CI: 0.04-0.61; $P$ = 0.026), systolic blood pressure (WMD, 2.62 mmHg; 95%CI: 1.35-3.89; $P$ < 0.001) and triglyceride (WMD, 0.25 mmol/L; 95%CI: 0.23-0.28; $P$ < 0.001).

**CONCLUSION:** Based on the cross-sectional data, SCH may be associated with an increased risk of the MS, which could be attributed to the increased risk of metabolic components.



**Key words:** Subclinical hypothyroidism; Metabolic syndrome; Meta-analysis

**Core tip:** A recent meta-analysis of individual data concluded that subclinical hypothyroidism (SCH) is associated with an increased risk of coronary heart disease (CHD) and CHD mortality. Meanwhile, it has been well recognized that the metabolic syndrome (MS) is associated with increased cardiovascular events and all-cause mortality. Our meta-analysis of cross-sectional data demonstrated that SCH may be associated with an increased risk of the MS, which may explain the relationship between SCH and increased risk of CHD.

Ye YC, Xie HZ, Zhao XL, Zhang SY. Subclinical hypothyroidism and the metabolic syndrome: A meta-analysis of cross-sectional studies. *World J Meta-Anal* 2013; 1(2): 90-96 Available from: URL: http://www.wjgnet.com/2308-3840/full/v1/i2/90.htm DOI: http://dx.doi.org/10.13105/wjma.v1.i2.90

## INTRODUCTION

Subclinical thyroid disease is defined biochemically and subclinical hypothyroidism (SCH) occurs when serum thyroid-stimulating hormone (TSH) concentrations are raised and serum thyroid hormone concentrations are normal[1].

Over the past several decades, a plethora of publications has established that SCH is associated with cardiovascular disease and a meta-analysis of individual data by Rodondi *et al*[2] concluded that SCH is associated with an increased risk of coronary heart disease (CHD) and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of 10 mIU/L or greater.

The metabolic syndrome (MS) is a cluster of multiple cardiovascular risk factors, including central obesity, glucose intolerance, diabetes, dyslipidemia and elevated blood pressure[3]. It has been well recognized that the MS is associated with increased cardiovascular events and all-cause mortality[4]. Recently, several cross-sectional studies have investigated a potential relationship between SCH and the MS, with conflicting findings[5-10]. To clarify this issue, we performed a meta-analysis of the published cross-sectional data in a general population to determine the association between SCH and the MS.

## MATERIALS AND METHODS

We designed a protocol that detailed the objective of our analysis, the criteria for study inclusion/exclusion, the assessment of study quality, the primary outcome and the statistical methods in accordance with the meta-analysis of observational studies in epidemiology[11] and PRISMA statements[12].

### Data sources and searches

We conducted a search of MEDLINE (1950 to July 2012) and EMBASE (1966 to July 2012) *via* EMBASE.com to identify all cross-sectional studies of a general population involving SCH and the MS [search strategy: (1) "hypothyroidism"/exp OR hypothyroidism; (2) "thyroid dysfunction"/exp OR thyroid dysfunction; (3) "thyroid disease"/exp OR thyroid disease; (4) "thyrotropin"/exp OR thyrotropin; (5) "thyroid stimulation hormone"/exp OR thyroid stimulation hormone; (6) "MS x"/exp OR MS x; (7) "MS"/exp OR MS; (8) 1 OR 2 OR 3 OR 4 OR 5; (9) 6 OR 7; (10) 8 AND 9], as well as a search of the Cochrane Database for Systemic Reviews. In addition, we performed a manual search of the literature using the references of original manuscripts, reviews and meta-analyses.

### Study selection

Two reviewers (Ye YC and Xie HZ) independently determined the study eligibility. Disagreements were resolved by consensus. The eligibility criteria for study inclusion were: (1) cross-sectional studies; (2) studies of a general population; (3) studies that reported the numbers of participants with the MS from among subjects with SCH and euthyroid; and (4) completely published studies (exclusive of unpublished material and abstracts). No language restriction was imposed. The κ value between two reviewers (Ye YC and Xie HZ) was 0.97 for the first screen (based on title and abstract) and 1.0 for the full-text screen.

### Data extraction

Data extraction was carried out independently by two authors in duplicate (Ye YC and Xie HZ). Disagreements were resolved by discussion between the two reviewing authors. From each included study, information was extracted on: (1) the characteristics of the study population; (2) the criteria for the MS; (3) TSH reference; (4) the numbers of participants with the MS in SCH and euthyroid groups; and (5) the components of the MS in SCH and euthyroid groups [including waist circumference, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose, triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C)].

### Risk of bias

Risk of bias was described and judged in following domains[13]: (1) Define the source of information (survey, record review); (2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; (3) Indicate time period used for identifying individuals; (4) Indicate whether or not subjects were consecutively enrolled if not population-based; (5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; (6) Describe any assessments undertaken for quality assurance purposes (*e.g.*, test/retest of primary outcome measurements); (7) Explain any individual exclusions from analysis; (8) Describe how confounding was assessed and/or controlled; (9) If applicable, explain how missing data were handled in the analysis; and (10) Summarize individual response rates and completeness of data collection. The judgments were assessed independently by two authors (Ye YC and Xie HZ) based on the published report and protocols of the studies. Disagreements were resolved by consensus. The judgments involved the answers "yes" (indicating a low risk of bias), "no" (indicating a high risk of bias), and "unclear" (if risk of bias is unknown or if an entry is not relevant to the study).

### Statistical analysis

The primary outcome was the unadjusted OR for the MS between the SCH and the euthyroid group. The secondary outcomes were the weighted mean difference (WMD) of the components of the MS between the SCH and the euthyroid group. The pooled unadjusted ORs and WMD for the outcomes were calculated using fixed effects models since there may be potential heterogeneity among the studies. The heterogeneity between the results of different studies was examined using $\chi^2$ tests for significance (a $P$-value < 0.10 was considered to be statistically significant) and the inconsistence was examined using $I^2$ tests. Subgroup analysis was used to explore the potential race heterogeneity (Chinese population and non Chinese population). Sensitivity analysis was used to explore the degree to which the main findings of our meta-analysis were affected by individual studies. Publication

**Table 1 Characteristics of included studies**

| Studies | Age (yr) | Male (%) | MS criteria | Sample size | Definition of SCH | Euthyroid | | | SCH | | | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | No. | MS | mTSH | No. | MS | mTSH | | |
| Hergenç *et al*[5] | 51.99 | 46.70 | NCEP /ATPⅢ | 488 | TSH > 4.2 μU/mL | 465 | 193 | 1.12 | 23 | 10 | 7.54 | Age > 34 yr | NA |
| Garduño-Garcia Jde *et al*[6] | 42.3 | 48.80 | NCEP /ATPⅢ | 3033 | TSH: 4.5-10 mIU/L FT4: 10-25 pmol/L | 2771 | 876 | NA | 262 | 84 | NA | Aged 18-70 yr | Thyroid disease, diabetes, cardiovascular disease, cerebral vascular disease, amputations, pregnancy, corticosteroid use, active liver disease, and renal dysfunction |
| Lai *et al*[7] | NA | NA | NCEP /ATPⅢ | 6254 | TSH > 5.0 μU /mL Normal FT4 | 6123 | 1871 | NA | 131 | 43 | 8.5 | Age > 65 yr | Taking medications for control of glucose, blood pressure, dyslipidemia, and thyroid function |
| Lai *et al*[8] | 45.1 | NA | China Diabetes Society | 1385 | TSH > 4.8 mIU/L Normal FT3/FT4 | 1283 | 238 | NA | 102 | 25 | NA | Aged 18-85 yr | History of thyroid disease; Taking medication such as thyroxine/antithyroid drugs, glucocorticoid, antiepileptic and contraceptive drugs; Pregnant/within the first year of postpartum period; Overt hypothyroidism/ hyperthyroidism |
| Liu *et al*[9] | 48.9 | 38.20 | International Diabetes Federation | 6339 | TSH > 4.5 mIU/L Normal FT3/FT4 | 5801 | 1236 | 2 | 538 | 138 | 6.5 | Aged 20-88 yr | Pregnant; Severe renal, liver or heart failure, or abdominal ascites; Taking medicines influencing thyroidal function |
| Waring *et al*[10] | 73.6 | 47 | NCEP /ATPⅢ | 2047 | TSH > 0.35 mIU/L | 1779 | 561 | NA | 268 | 98 | NA | Aged 70-79 yr | Diabetes; Taking medication such as amiodarone, lithium and antithyroid medications |

NCEP/ATPⅢ: National Cholesterol Education Program/Adult Treatment Panel Ⅲ; TSH: Thyroid-stimulating hormone; MS: Metabolic syndrome; SCH: Subclinical hypothyroidism; FT4: Free thyroxine; FT3: Free triiodothyronine; NA: Not available; mTSH: mean/median thyroid-stimulating hormone level.

bias was assessed by the Begg's funnel plot and the Egger weighted regression statistic, with a value of $P < 0.10$ indicating significant publication bias among the included studies[14,15]. All statistical analyses were performed using STATA 11.0 (STATA, TX, United States).

## RESULTS

### Study identification

In total, 515 studies were retrieved from the initial search and 17 studies were reviewed in full text. Six cross-sectional studies investigating a total of 19546 participants were included in the meta-analysis (Figure 1).

### Study characteristics

The analysis included a total of 1324 SCH and 18222 euthyroid is imparticipants. In the individual studies, the sample size ranged from 488 to 6339. The reported mean age of the participants ranged from 42.3 to 73.6 years. Each study included both males and females. Table 1 presents a summary of the characteristics of the study population, the criteria for the MS, the TSH reference and the prevalence of the MS in SCH and euthyroid groups. Of the six studies included, four provided data on the components of the MS in SCH and euthyroid groups (Table 2). The results of quality assessment of included studies (risk of bias) were summarized and are presented in Figure 2.

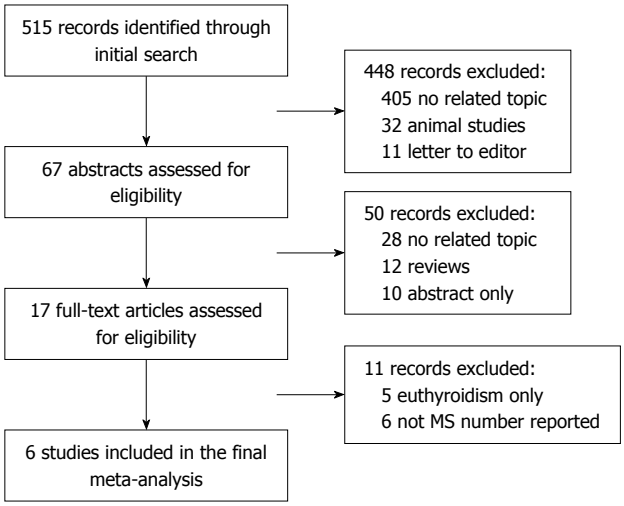


**Figure 1 Flowchart of study selection.** MS: Metabolic syndrome.

### Data analysis of outcomes

In total, 4975 of the 18222 participants (27.30%) in the euthyroid group fulfilled the criteria for the MS, compared to 398 of the 1324 participants (30.06%) in the

**Table 2 Components of the metabolic syndrome in each study**

| Studies | Thyroid function | *n* | Waist (cm) | BMI (kg/m$^2$) | SBP (mmHg) | DBP (mmHg) | FBG (mmol/L) | TG (mmol/L) | HDL-C (mmol/L) |
|---|---|---|---|---|---|---|---|---|---|
| Hergenç *et al*[5] | Euthyroid | 465 | 95.4 ± 10.5 | 29.3 ± 4.5 | 126.5 ± 20.6 | 80.9 ± 10.9 | 5.77 ± 2.30 | 1.92 ± 1.24 | 1.14 ± 0.32 |
| | SCH | 23 | 93.0 ± 10.5 | 29.0 ± 4.2 | 121.6 ± 23.8 | 78.8 ± 13.2 | 5.66 ± 1.51 | 1.81 ± 1.11 | 1.16 ± 0.30 |
| Garduño-Garcia | Euthyroid | 2771 | 94.21 ± 11.18 | 28.69 ± 4.5 | 115 ± 15.12 | 77.29 ± 10.68 | 4.90 ± 1.16 | 2.29 ± 1.73 | 1.10 ± 0.29 |
| Jde *et al*[6] | SCH | 262 | 94.06 ± 11.18 | 28.98 ± 5.1 | 118 ± 16.23 | 78.22 ± 10.87 | 4.91 ± 0.973 | 2.59 ± 4.03 | 1.13 ± 0.29 |
| Lai *et al*[8] | Euthyroid | 1283 | 80.8 ± 10.3 | 24.3 ± 3.6 | 123 ± 18 | 79 ± 11 | 5.22 ± 0.03 | 1.47 ± 0.03 | 1.33 ± 0.37 |
| | SCH | 102 | 80.7 ± 9.6 | 24.5 ± 3.3 | 122 ± 19 | 77 ± 11 | 5.12 ± 0.11 | 1.73 ± 0.12 | 1.26 ± 0.27 |
| Liu *et al*[9] | Euthyroid | 5801 | 80.4 ± 11.1 | 24.4 ± 6.6 | 126.8 ± 19.2 | 81.9 ± 11.3 | 5.2 ± 1.7 | 1.5 ± 1.6 | 1.3 ± 0.4 |
| | SCH | 538 | 81.1 ± 12.4 | 24.8 ± 3.9 | 130.2 ± 20.8 | 83.4 ± 12.0 | 5.3 ± 1.5 | 1.6 ± 1.7 | 1.3 ± 0.6 |

SCH: Subclinical hypothyroidism; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; TG: Triglyceride; HDL-C: High density lipoprotein cholesterol.

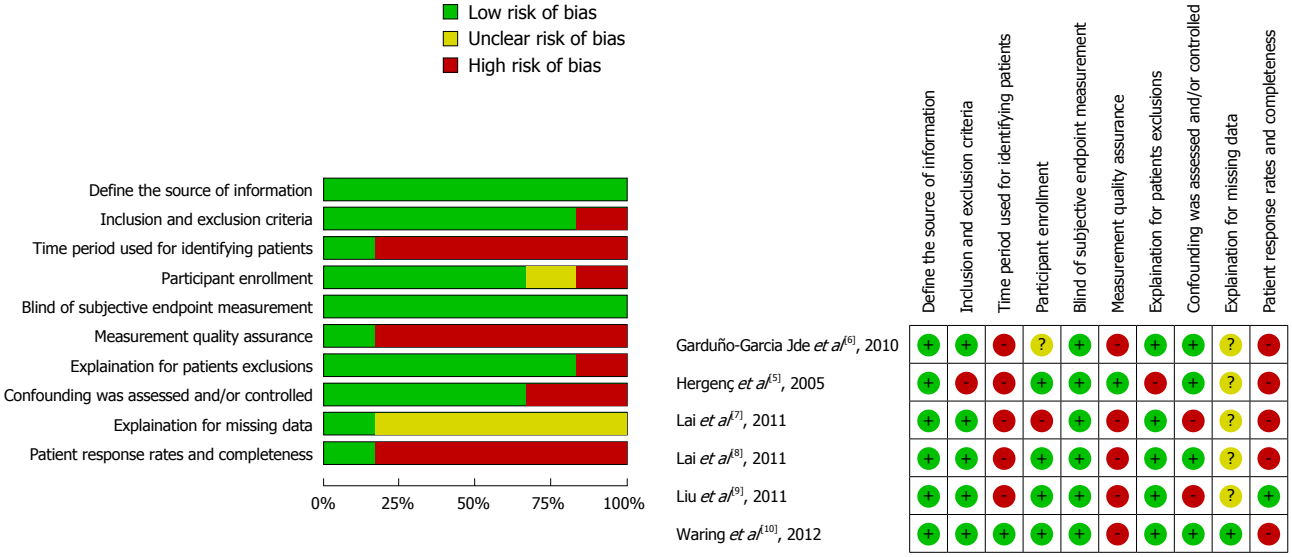


**Figure 2 Risk of bias assessment.**

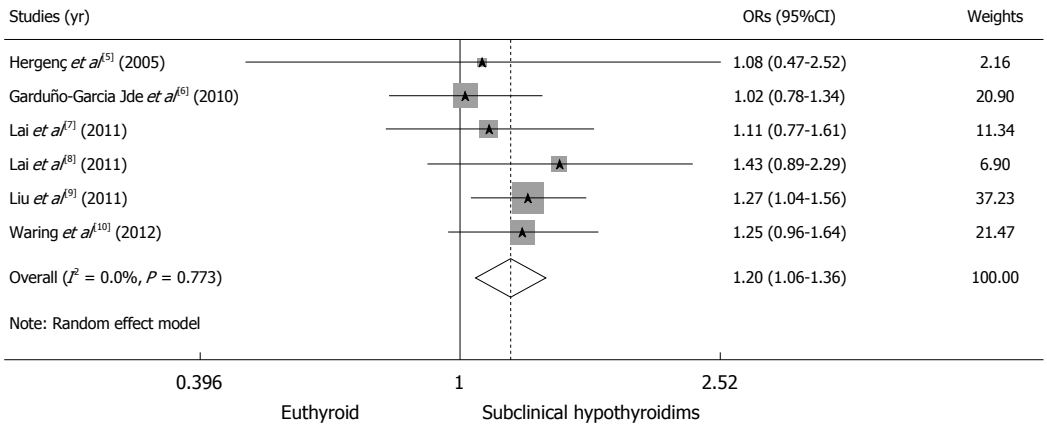


**Figure 3 Subclinical hypothyroidism *vs* euthyroid on pooled ORs for the metabolic syndrome.**

SCH group. The pooled risk of the MS is significantly higher in the SCH group than in the euthyroid group (OR, 1.20; 95%CI: 1.05-1.36; $P = 0.004$). We obtained a $\chi^2$ value of 2.53 ($P = 0.773$) and an $I^2$ value of 0%, indicating the absence of heterogeneity among the studies analyzed (Figure 3).

Further meta-analysis of the components of the MS showed that SCH was associated with increased BMI (WMD, 0.32 kg/m$^2$; 95%CI: 0.04-0.61; $P = 0.026$), SBP (WMD, 2.62 mmHg; 95%CI: 1.35-3.89; $P < 0.001$) and TG (WMD, 0.25 mmol/L; 95%CI: 0.23-0.28; $P < 0.001$). The rest of the components, including waist circumfer-

**Table 3 Sensitivity analysis of the effect of exclusion of individual studies on pooled ORs with 95%CI**

| Studies excluded | Pooled ORs of remaining studies (95%CI) | *P* for OR | $I^2$ (%) | $\chi^2$ | *P* for $\chi^2$ |
|---|---|---|---|---|---|
| Hergenç *et al*[5] | 1.20 (1.06-1.36) | 0.004 | 0 | 2.47 | 0.650 |
| Garduño-Garcia Jde *et al*[6] | 1.25 (1.09-1.44) | 0.002 | 0 | 0.84 | 0.934 |
| Lai *et al*[7] | 1.21 (1.06-1.38) | 0.005 | 0 | 2.34 | 0.673 |
| Lai *et al*[8] | 1.18 (1.04-1.35) | 0.011 | 0 | 1.97 | 0.742 |
| Liu *et al*[9] | 1.15 (0.99-1.35) | 0.071 | 0 | 1.97 | 0.742 |
| Waring *et al*[10] | 1.20 (1.03-1.36) | 0.018 | 0 | 2.40 | 0.663 |

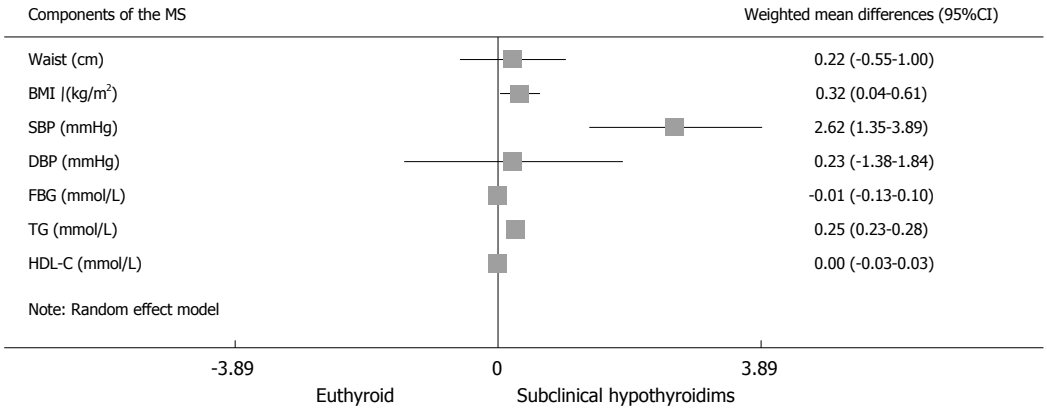


**Figure 4 Weighted mean differences for the components of the metabolic syndrome.** MS: Metabolic syndrome; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBG: Fasting blood glucose; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol.

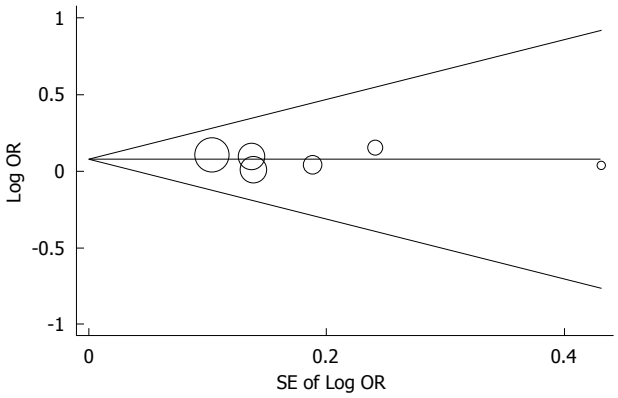


**Figure 5 Begg's funnel plot with pseudo 95%CI for publication bias.**

ence, DBP, fasting blood glucose and HDL-C, were not significantly different between the two groups (Figure 4).

The subgroup analysis indicated that the OR for the MS in Chinese studies did not significantly differ from that in non Chinese studies (OR for MS in Chinese studies: 1.256; 95%CI: 1.063-1.484; OR for MS in non Chinese studies: 1.130; 95%CI: 0.938-1.360, *P* for interaction = 0.404). The sensitivity analysis indicated that the pooled ORs excluding each individual study were comparable (Table 3). No significant publication bias was found after assessment using the Begg's funnel plot (*P* = 0.573) and the Egger weighted regression statistic (*P* = 0.833) (Figure 5).

## DISCUSSION

In this meta-analysis of 19546 participants from six cross-sectional studies of a general population, SCH was associated with an increased risk of the MS compared with being euthyroid. To our best knowledge, this is the first meta-analysis showing the relationship between SCH and the MS. The previous meta-analysis demonstrated a possible association between SCH and increase risk of CHD[2]. This association might be mediated by the effect of these risk factors because the MS is one of the established risk factors for cardiovascular disease[4,16]. However, whether this association between SCH and coronary heart is independent or dependent of MS is still unclear and further investigation is needed.

Even in euthyroid populations, the relationship between thyroid function and the MS has been well investigated, with results consistent with those of our meta-analysis. In a cross-sectional study in the Netherlands, free T4 levels within the normal reference range were significantly related to four of the five components of the MS (*P* for waist circumference = 0.038, *P* for TGs = 0.023, *P* for HDL-C = 0.007 and *P* for SBP = 0.019), independent of insulin resistance[17]. Park *et al*[18] found a close relationship between TSH and the MS in euthyroid postmenopausal women (adjusted OR for the MS 1.55; 95%CI: 1.26-1.89; *P* < 0.001).

It was previously reported that overt hypothyroidism was associated with the MS[19], presumably because of the associated hypercholesterolemia and hypertension[20]. The reason why SCH is associated with the MS could be also attributed to the increased risk of the components of the MS. In a study evaluating 27097 individuals > 40 years of age without a diagnosis of thyroid disease, serum TSH, even within the normal range, was positively associated

with BMI (*P* for trend in all BMI groups < 0.001)[21]. The relationship between blood pressure and thyroid function has also been well investigated but with conflicting findings[22-25]. A recent meta-analysis of seven cross-sectional studies concluded that SCH is associated with increased blood pressure, whereas subclinical hyperthyroidism is not[26]. Hypothyroidism has been associated with dyslipidemia, which is characterized by increased levels of total cholesterol and low-density lipoprotein cholesterol[27]. In the Colorado thyroid disease prevalence study, the total cholesterol, low-density lipoprotein cholesterol and TG levels of SCH subjects were significantly greater than the corresponding lipid levels in euthyroid subjects ($P < 0.001$ for total cholesterol and low-density lipoprotein cholesterol; $P = 0.02$ for TG), whereas no difference was found in HDL-C level[28]. Our meta-analysis of metabolic components has further confirmed these conclusions.

Another important issue is whether SCH should be treated with thyroid hormones or whether hormone replacement therapy could reduce the cardiovascular risk and mortality in SCH. A systematic review of randomized controlled trials showed that thyroid hormone replacement in SCH could improve the lipid profile (WMD for low-density lipoprotein cholesterol: -10.77 mg/dL; 95%CI: -21.57-0.04; $P = 0.051$)[29] and recent data from a cohort study indicated that treatment of SCH with levothyroxine was associated with less ischemic heart disease in younger individuals compared to those without treatment (adjusted hazard ratio 0.61; 95%CI: 0.39-0.95)[30]. Since our meta-analysis indicated a higher risk of the MS in SCH, screening and treatment of these metabolic components are necessary to further reduce the risk of cardiovascular events.

It is notable that the included study from Waring *et al*[10] reported not only cross-sectional data but also prospective data, making it the only prospective study on SCH and the MS in the literature. After 6 years of follow-up, the risk of the MS in SCH individuals with a TSH > 10 mIU/L was similar to that in the baseline cross-sectional analysis but with a wider confidence interval (OR for cross-sectional analysis, 2.3; 95%CI: 1.0-5.0; OR for prospective analysis, 2.2; 95%CI: 0.6-7.5). However, this study seemed to be underpowered because a very small number of participants with marked SCH were included[10].

Our study has several limitations. Firstly, although our heterogeneity test showed no statistically significant heterogeneity among studies, it is still impossible that our final results would be confounded by the different definitions of SCH and MS among the included studies, as well as the different inclusion/exclusion criteria. Secondly, this is a study-level and we used unadjusted OR instead of adjusted OR; thus, it is impossible to exclude the confounding effects of age, sex and race. Finally, although no statistically significant publication bias was detected in our analysis, we believe there may be data relevant to this topic that have never been published.

Our meta-analysis indicated that SCH may be associated with an increased risk of the MS, which is attributed to the increased risk of metabolic components. A large prospective cohort study is needed to further confirm the conclusion of our study.

## COMMENTS

### Background

Over the past several decades, a plethora of publications has established that subclinical hypothyroidism (SCH) is associated with cardiovascular disease. Meanwhile, it has been well recognized that the metabolic syndrome (MS) is associated with increased cardiovascular events and all-cause mortality.

### Research frontiers

Is SCH associated with a higher risk of the MS?

### Innovations and breakthroughs

This meta-analysis of 6 cross-sectional studies with 19546 participants indicated that SCH may be associated with increased risk of the MS, which is attributed to the increased risk of metabolic components.

### Applications

It may be necessary to screen for the MS in SCH individuals in clinical practice.

### Terminology

SCH occurs when thyroid-stimulating hormone levels are elevated but thyroxine (T4) and triiodothyronine (T3) levels are normal. MS is a name for a group of risk factors that occur together and increase the risk for coronary artery disease, stroke and type 2 diabetes.

### Peer review

This paper reports the results of a meta-analysis of observational studies evaluating the association between SCH and MS and its individual components. Overall methodology is correct and the results are very interesting and valuable.

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*World J Meta-Anal* 2013 August 26; 1(2): I-V
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### *Launch date*

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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